

IDSP PROGRESS REPORT
ON
HEALTH EFFECTS OF ALUMINUM
IN THE WORKPLACE

INDUSTRIAL DISEASE STANDARDS PANEL
COMITÉ DES NORMES EN MATIÈRE DE MALADIES
PROFESSIONNELLES

OCTOBER, 1989



Ontario
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de l'Ontario

Industrial
Disease
Standards
Panel

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October 20, 1989

Dr. R.G. Elgie
Chairman
Workers' Compensation Board
2 Bloor Street East, 20th Floor
Toronto, Ontario
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Dear Dr. Elgie:

In a letter dated December 16, 1988, you requested that the Industrial Disease Standards Panel investigate the possibility that workplace exposure to aluminum results in industrial disease. I am writing at this time to provide a progress report concerning the Panel's investigation of this issue. The paragraphs that follow were reviewed at Panel's October 18th Meeting and endorsed by all Members present (Panel Members Buck, Chong, Dupré, Gibson, Hess, Jolley and Miller).

Panel staff have produced a literature review of the scientific evidence on aluminum health effects. This review has been vetted by recognized external experts on the health effects of aluminum in the workplace. These experts were: Dr. N.M. Cherry (Neurobehavioral Research Unit, McGill University; Dr. W.K.C. Morgan (University Hospital, University of Western Ontario); Dr. P.S. Spencer (Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University); and Dr. G. Thériault, School of Occupational Health, McGill University). These experts supported the conclusions of the literature review and made specific suggestions designed to enhance its comprehensiveness. These suggestions are appended, along with the revised literature review, to this letter.

The scientific evidence linking aluminum exposure with disease that

emerges from this literature review can be summarized as follows:

DISEASE	INDUSTRY AND/OR EXPOSURE
A. Lung Disease	
1. Pulmonary Fibrosis	Pyrotechnics Industry and mainly of historical interest only (free aluminum coated in mineral oil)
2a. Pulmonary Alveolar Proteinosis (PAP)	Non-specific responses to high levels of all dusts of which aluminum may be a component
2b. Desquamative Interstitial Pneumonia (DIP)	
2c. Pulmonary Granulomatosis (PG)	
B. Neurological Disease	
3. Dialysis Encephalopathy Syndrome (DES)	Aluminum antacids or aluminum-containing dialysis water (and only in persons with renal failure on or not on dialysis)

Your letter of December 16th raised the aluminum health issue in the context of "the assertion that workers with elevated serum aluminum levels are experiencing neurological and other health problems. The workers are exposed to aluminum dust, the airborne levels of which are below the level currently established by the Ministry of Labour."

The assertion and the workers to whom your letter refers involve two Ontario aircraft plants: the McDonnell Douglas plant in Mississauga and the Boeing-de Havilland plant in Downsview. Our literature review, as summarized above, sheds no light on the possibility of aluminum-related disease in the aircraft industry, and for that matter in secondary manufacturing generally.

With respect to lung disease, the literature review reveals that pulmonary fibrosis was limited to the pyrotechnics industry in the secondary manufacturing sector during the forties and fifties. During that time, a method of manufacturing explosives (using finely divided aluminum powder coated with a non-polar mineral oil) was briefly adopted in England, Germany and Sweden and was subsequently discontinued. The reported cases of pulmonary fibrosis (or 'aluminosis') from this industry resulted from the inhalation of this

mineral oil-coated free aluminum. In the watery tissue of the lung, the coating would dissolve and an exothermic reaction would result from the contact of the unbound aluminum with water. The lung fibrosis likely resulted from the heat released during this reaction.

As for pulmonary alveolar proteinosis (PAP), desquamative interstitial pneumonia (DIP) and pulmonary granulomatosis (PG), the literature review indicates that these lung diseases have resulted, whether in primary or secondary manufacturing industries, from generalized and severe dust exposure. Aluminum is a prominent constituent of most dust. However, the literature considers that PAP, DIP and PG result from the severity of the generalized dust insult and not from the aluminum.

With respect to neurological disease, the literature review confirms the existence of a single aluminum-related condition called dialysis encephalopathy syndrome (DES). But this condition, as its name indicates, has no association whatsoever with occupational exposure of any kind. It arises among patients suffering kidney failure either from the ingestion of aluminum-containing antacids, or from the presence of aluminum in the dialysate or water used during dialysis to cleanse the blood.

Beyond the literature review, the Panel has reviewed a substantial proportion of the claims for compensation for industrial disease from both plants filed with the Board during the 1986-88 time period. This exercise uncovered no evidence of either lung disease or central nervous system (CNS) disorders which was explainable by aluminum exposure. However, there have been numerous instances of irritations (to the skin, eyes, lungs, etc.) arising from acute solvent exposure. And several claims were identified for symptoms of CNS problems (viz. dizziness, giddiness, headaches, etc.) also arising from acute solvent exposure.

The fact that the reviews of the scientific literature and the disease claims from the aircraft plants have not uncovered evidence linking aluminum to adverse health effects in manufacturing is not conclusive.

There is the possibility that currently ongoing research may yield evidence associating aluminum exposure in the workplace with diseases or their precursors. The Northern Ontario Miners' Study, under the direction of University of Toronto researchers, is examining all possible health effects among these miners including any possible evidence linking neurological disorders with aluminum prophylaxis. The evidence from this study may be supplemented by a reexamination of the data in the Mining Master File previously maintained by the Board which may contain some hitherto unidentified association between aluminum prophylaxis treatment of Ontario miners and non-malignant

respiratory diseases. The Panel is aware of research being conducted under the auspices of the Aluminum Association to examine the relationship between occupational aluminum dust and fume exposure and blood and urine aluminum concentrations.

The Panel is closely monitoring all these initiatives. In addition, the Panel is aware that the Ministry of Labour is exploring a possible health study of aircraft workers.

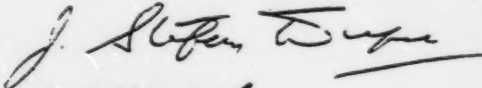
Whether or not the above activities yield further light on aluminum as a disease-producing agent, what the literature and claims' reviews do suggest is that allegations of disease in the aircraft industry should be investigated in relation to substances other than aluminum. The Panel has visited the McDonnell Douglas and Boeing-de Havilland plants and can confirm that concern and anxiety among aircraft workers are genuine. The Panel therefore has an interest in exploring the extent of the diseases and symptoms that are at the root of these anxieties.

In pursuing this interest, the Panel has learned that, at the Boeing Company in Seattle, Washington, there are alleged neurological disorders among aircraft workers which have not been associated with aluminum exposure. Confirmation of diseases or symptoms in the aircraft industry is vitally important, as is an exploration of a variety of possible disease-inducing agents in that industry. Such agents might be any of a number of solvents, glues or resins. It has already been confirmed that a serious matter of isocyanate exposure and consequent occupational asthma has existed in this industry. It is well known that exposure to some of these chemical substances can lead to cognitive deficits and other sorts of neurobehavioural and neuropsychological problems. The Panel is also aware that, in an effort to achieve greater fuel economy through the use of lighter weight components, the aircraft industry is turning increasingly to the use of graphite composites as substitutes for aluminum. These composites are often in the form of resin-impregnated fibres. Their use in the aircraft industry has been reported to be associated with neurological disorders of the sort which have been alleged in our own Ontario aircraft industry. Accordingly, a delegation of the Panel intends to visit the Boeing Company in Seattle at the earliest opportunity to meet with labour and management representatives and with researchers from the University of Washington. This visit will shed light on the issue of alleged neurological disorders among aircraft workers arising from exposure to resin-impregnated graphite composites.

As for the Ontario aircraft plants, the Panel is examining Ministry hygiene surveys for the nature and extent of all exposure to potentially hazardous substances, especially neurotoxic substances. The Panel is also assessing the availability of clinical information that has been collected from workers in these plants.

To conclude, the current state of Panel's progress with what began as a Board reference concerning aluminum-related disease in the workplace indicates the need to work toward an eventual report concerning health effects among Ontario aircraft workers resulting from exposures to a variety of substances. Through this letter to you, the Panel wishes to share the extent of its current evidence and of proposed initiatives with the Board and all interested parties.

Yours sincerely,



J. Stefan Dupré
Chairman

Attachments:

1. Literature Review (Health Effects of Aluminum in the Workplace, L.F. Smith, Industrial Disease Standards Panel, September 9, 1989).
2. Health Effects of Aluminum in the Workplace: Reviewers' Comments.

**Workers' Compensation Board of Ontario/
Commission des accidents du travail de l'Ontario**

IN THE MATTER OF Section 86(p)
of the Workers' Compensation Act
R.S.O. 1980, c. 539, as amended;

AND IN THE MATTER OF the
IDSP Progress Report on
Health Effects of Aluminum in the Workplace

REQUESTS FOR SUBMISSIONS

Section 86(p) of the Workers' Compensation Act provides for the creation of an Industrial Disease Standards Panel (the Panel). It is the function of the Panel to:

- (a) investigate possible industrial diseases;
- (b) make findings as to whether a probable connection exists between a disease and an industrial process, trade or occupation in Ontario;
- (c) create, develop and revise criteria for the evaluation of claims respecting industrial diseases; and,
- (d) advise on eligibility rules regarding compensation for claims respecting industrial diseases.

In a letter dated December 16, 1988, Dr. Elgie, Chairman, Workers' Compensation Board, requested the Industrial Disease Standards Panel investigate the possibility that workplace exposure to aluminum results in industrial disease.

On October 20, 1989, Dr. Dupré, Chairman, Industrial Disease Standards Panel provided the Workers' Compensation Board with a progress report on the health effects of aluminum in the workplace in the form of the letter which follows. The attachments to the letter consisted of two extensive documents:

- (i) Literature Review (Health Effects of Aluminum in the Workplace, L.F. Smith, Industrial Disease Standards Panel, September 9, 1989).
- (ii) Health Effects of Aluminum in the Workplace: Reviewers' Comments.

These documents are available on request from the Industrial Disease Standards Panel and can be obtained by contacting Dr. James Heller, Executive Administrator, Industrial Disease Standards Panel, 10 King Street East, 7th Floor, Toronto, Ontario M5C 1C3 - 965-5056.

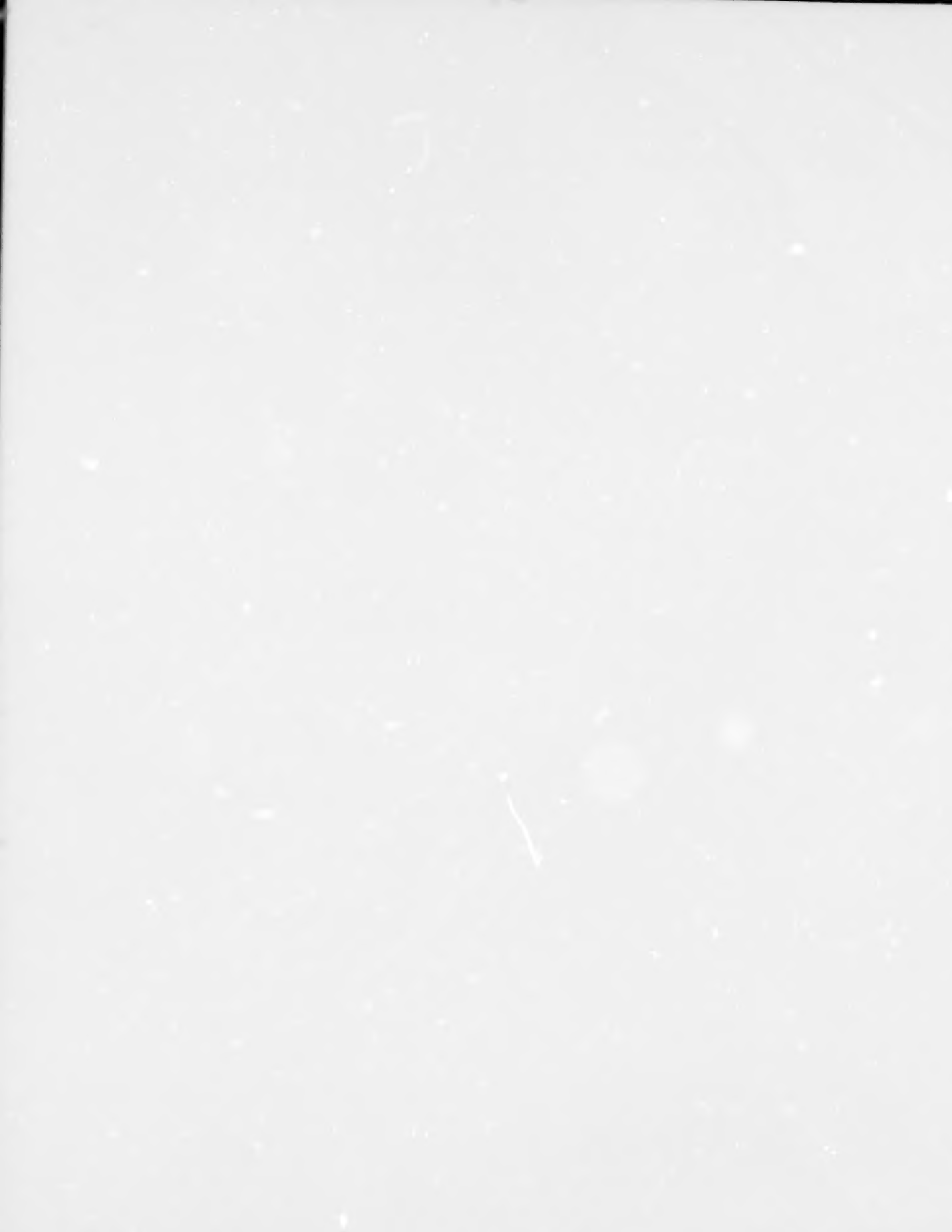
In accordance with sub-section 86p(11) of the Workers' Compensation Act, the Board has published this notice. Comments, briefs and submissions must be filed with the Workers' Compensation Board within six months of the date of this notice. All comments, briefs and submissions related to this progress report should be sent to Ms. Linda Angove, Secretary of the Board, Workers' Compensation Board, 2 Bloor Street East, 20th Floor, Toronto, Ontario M4W 3C3.

The final report of the Industrial Disease Standards Panel on the Health Effects of Aluminum in the Workplace will be published upon receipt by the Workers' Compensation Board and, in accordance with sub-section 86p(11) of the Workers' Compensation Act, the Board will request written comments, briefs and submissions from any interested parties.

HEALTH EFFECTS OF ALUMINUM IN THE WORKPLACE

Lesbia F. Smith

Industrial Disease Standards Panel
September 9, 1989



ACKNOWLEDGMENTS

The author gratefully acknowledges the comments of a previous draft of this paper made by the reviewers listed below. These comments have been incorporated into the present version.

- Nicola M. Cherry Associate Professor, Neurobehavioral Research Unit, School of Occupational Health, McGill University;
- .. W. Keith C. Morgan Chest Diseases Unit, University Hospital, University of Western Ontario;
- Peter S. Spencer Director, Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University;
- Gilles Theriault Professor and Director, School of Occupational Health, McGill University.

HEALTH EFFECTS OF ALUMINUM IN THE WORKPLACE

TABLE OF CONTENTS

EXECUTIVE SUMMARY

1. INTRODUCTION

2. CHEMICAL AND PHYSICAL PROPERTIES

3. ALUMINUM BALANCE

3.1 GENERAL PRINCIPLES

3.2 INTAKE

3.3 UPTAKE

3.3.1 UPTAKE FROM THE GASTROINTESTINAL TRACT

3.3.2 UPTAKE FROM THE SKIN

3.3.3 UPTAKE FROM THE LUNG

3.4 TRANSPORT, TISSUE DISTRIBUTION, EXCRETION

3.5 BIOLOGIC MONITORING AND MEDICAL SURVEILLANCE

3.6 SUMMARY

4. HEALTH EFFECTS

4.0 GENERAL

4.1 THE SKIN

4.2 THE LUNG

4.2.1 CASE REPORTS

1) pulmonary fibrosis (aluminosis); 2) pulmonary alveolar proteinosis and Al dust; 3) desquamative interstitial pneumonia; 4) pulmonary granulomatosis; 5) pulmonary fibrosis and alumina fibers; 6) pulmonary fibrosis and abrasives in Ontario (Shaver's disease)

4.2.2 EPIDEMIOLOGY OF LUNG DISEASE IN ALUMINUM MINING, PROCESSING AND HANDLING

1) general; 2) smelter workers

4.2.3 SUMMARY

4.3 THE CENTRAL NERVOUS SYSTEM AND AL

4.3.1 CASE REPORTS

4.3.2 THE DEMENTIAS

1) general; 2) dialysis dementia; 3) amyotrophic lateral sclerosis and parkinsonism-dementia syndrome; 4) Alzheimer's disease (senile dementia of the Alzheimer type)- hypotheses regarding the cause of SDAT (heredity, immunity, transmissible agent, metal toxicity (aluminum)), epidemiology of non-dialysis dementia [ecological studies, case-control studies, occupational mortality studies]

EXECUTIVE SUMMARY

1. The aluminum (Al) molecule is highly reactive, does not figure in normal biological processes, is ubiquitous in nature and does not tend to accumulate in humans over the course of a lifetime if normal elimination is maintained. Selective deposition may occur at the subcellular level under certain conditions without any significant increase in the corresponding tissue concentration. Al metabolism has been studied with radioisotopes of other metals with similar properties and in disease states where normal Al excretion is impaired (renal failure) or where there has been other organ failure (respiratory or neurological disease).
2. The absorption of Al from diet and medications takes place through the gastrointestinal tract. Al absorption through the gut varies considerably and is influenced by: diet - certain compounds in food stuffs (glycine, maltol) may enhance Al absorption by enabling Al to be transported across the mucosal membrane into the blood; and physiologic state - hormone status, fasting, iron deficiency, other dietary components, etc. Al absorption is enhanced by iron deficiency (which increases the available transferrin, the iron-bearing protein) in fasting organisms; is decreased in the presence of phosphate; and may be promoted by parathyroid hormone.

Systemic absorption of Al from antiperspirants does not occur. Beyond one case report of dermal application of Al oxide cream

which remains controversial, there is no evidence to support skin uptake.

3. Al from welding fumes is absorbed through the lungs. Body retention of Al from welding fumes varies from days to months depending on the duration of occupational exposure. Inhaled Al salts (oxides) are not absorbed systemically but may be coughed up and swallowed.
4. Transferrin, albumin and possibly other plasma proteins transport Al to tissues. The kidney excretes the unbound, ultrafilterable fraction from the plasma.
5. Al distributes throughout the body; the greatest concentrations occur in the lung followed by bone. However, because of the greater overall bone mass, 50% of the total body content of Al by weight is in bone while 25% is in lung tissue. Al in the lungs more likely arises from inhalation than from gastrointestinal absorption. Healthy individuals have about 30 to 50 mg of Al in their bodies. Normal dietary intake of Al varies considerably. If one assumes an average intake of 20 mg per day, no retention and a normal urinary excretion of 20 to 50 ug/day, then the (calculated) normal uptake fraction is between 0.1 and 0.3%. This fraction drops to 0.01% with much larger oral doses (e.g. from antacids), assuming again that urinary excretion of Al is a measure of intestinal absorption and there is little or no retention.

6. Plasma and serum Al are not quantitative measures of exposure or of body burden in the normal individual. In persons with impaired elimination (kidney failure), plasma Al is raised and has a small positive correlation with bone Al where its presence can be used as an indicator of body burden and treatment. In vivo measures of body burden in individuals with normal renal function are not available. The use of desferrioxamine (DFO) to assess body burden in persons with normal renal function remains investigational. The sensitivity, specificity and predictive value of DFO as a diagnostic tool for measuring Al body burden in normal humans has not been fully evaluated.
7. Aluminum mining, smelting (electrolytic reduction) and some secondary uses are associated with a variety of health effects most of which do not arise from Al itself. Bauxite mining is associated with bauxite lung, attributable to silica. Electrolytic reduction releases fluoride fumes, exposure to which may produce fluorosis. Exposure to pitch fumes (i.e. coal tar pitch volatiles) which are released during the forming of electrodes in the Soderberg method is associated with lung and bladder cancer; the latter is a compensable disease in Quebec. Pitch fume exposure is also related to a skin condition (telangiectases) compensable in Quebec. Skin sensitivity to aluminum occurs rarely in the workplace. Exposure to low temperature transitional forms of alumina in smelting theoretically may occur. However, these forms of alumina have produced fibrosis only in controlled animal models which introduce

the alumina forms directly into the lungs through the trachea. This response has never been documented in humans.

8. Aluminum powder as used in the pyrotechnics industry is associated with severe pulmonary fibrosis only when the powder coating used is a non-polar mineral oil, and not animal fat (stearin). Single case reports of several other lung conditions question the causal role of aluminum. These conditions are: pulmonary alveolar proteinosis (PAP), (aluminum) fiber induced pulmonary fibrosis, pulmonary granulomatosis (PG) and desquamative interstitial pneumonitis (DIP). In the last, the role of Al is speculative. PG is not related to aluminum. PAP results as a non-specific response to an increased load of dust of many types. Metallic aluminum powder as used in the prophylaxis of silicosis in Ontario has not been shown to produce lung fibrosis. Shaver's disease and pulmonary disease due to handling abrasives (corundum) result from exposure to cristobalite silica.
9. Two case reports of neurological disease (encephalopathy) and high body and brain aluminum levels are unique in the literature. One case had pulmonary fibrosis and occupational exposure to Al pyro powder (coated with mineral oil); the other had no occupational exposure and no pulmonary disease but was a severe alcoholic. The clinical course of the former was acute, of the latter chronic. Both had seizures. However, the role of Al in the neurological picture of these cases remains uncertain.

10. Al content in the bone and in the brain of renal failure patients who develop dialysis encephalopathy syndrome, a neurological disorder among long-term dialysis patients, is consistently high, higher than in dialysis patients who do not develop the disease. These patients also have elevated total body aluminum stored in bone and a high proportion also have bone disease (osteodystrophy). The source of the Al is Al-containing antacids used to bind phosphates in the gut, and low concentrations of Al present in dialysis water which has not been treated by deionization or reverse osmosis. The causal role of Al in dialysis encephalopathy syndrome (DES), is not disputed. However, not all dialysis patients on the same treatment will develop the DES while some patients who have never been on dialysis do develop the disease. Factors which differentiate those at risk from others are still not completely understood.

11. There are two major environmental hypotheses regarding the cause of Western Pacific ALS-PD complex (i.e. amyotrophic lateral sclerosis-parkinsonism dementia syndrome). The brain of persons with ALS-PD contains elevated levels of Al. These hypotheses include toxicity from a plant toxin (Cycad seed), or an interaction of aluminum (in soil, water and foods) with low calcium and magnesium in the diet. Cycad seeds are used as medicine or food in Guam and as medicinals elsewhere in the Western Pacific endemic areas. Individuals from the endemic areas (including Guam, the Kii peninsula of Japan and

western New Guinea) may develop the disease long after their departure suggesting a latency period between exposure and disease. The decreasing incidence of ALS-PD in endemic areas is hypothesized to be related to the changes which have occurred in the local diet and in the use of the Cycad seed as a medicine.

12. The evidence for causality for the cycad toxin in ALS-PD is experimental and epidemiological (ecological studies). The evidence linking Al is primarily epidemiological (ecological studies). The presence of elevated Al levels in the brain of individuals with degenerative brain disorders remains to be differentiated as a primary (causal) or secondary (resulting from the disease) phenomenon.

13. Alzheimer's disease (SDAT) is well defined pathologically by the presence of senile plaques and neurofibrillary tangles in the brain tissue of SDAT cases. Al is consistently elevated in the tangle-bearing neurons of these patients. The Al occurs in particular regions of the nuclear chromatin (DNA) of the neurons in the cortex and hippocampus.

14. Several hypotheses have been formulated to explain the occurrence of SDAT: inheritance (autosomal, familial, sporadic); transmissible infective agent; autoimmune disorder; and aluminum toxicity. Ecological studies and case control studies point to a variety of associated risk factors for SDAT. Cerebral injury and

familial aggregation consistently appear as a risk factors in case-control studies. Al has been examined as a risk factor only recently and no case-control study to date clearly supports an association between exposure to Al and SDAT. The role of aluminum is still under considerable debate and investigation. Many questions remain unanswered.

HEALTH EFFECTS OF ALUMINUM IN THE WORKPLACE

1. INTRODUCTION

The abundant metal, Al, is not essential to human life in that it does not figure in any normal biological system. However, recent work has shown that under certain conditions, it is toxic to plants and animals, and its properties are described as "incompatible with fundamental life processes" (Ganrot, 1986). The behaviour of any substance in the body is related to its intrinsic chemical, electrical and physical properties. In order to understand the biological nature of health effects which may occur in man, the subject of this review, it is necessary to understand the nature of Al and its compounds and their behaviour in biological systems. This review begins, therefore, with a description of the biological mechanisms linking Al exposure to uptake and retention in the organism and its effects on target tissues.

2. CHEMICAL AND PHYSICAL PROPERTIES

Free Al is a highly charged atom of small size (radius of 0.51 Angstroms or 0.51×10^{-8} cm) which in nature always carries a charge of -3. The Al molecule is very reactive, readily combining with a host of other atoms and molecules. In water, Al reacts with (hydrolyses) water molecules to form an acid solution (Ganrot 1986). Complex molecules of the hydroxide form slowly, crystallizing as aluminum hydroxide $[Al_2(OH)_3]$ which is the chemical form in various aluminum ores (gibbsite, bayerite.

boehmite) (Ganrot, 1986). Aluminum also binds to oxygen and occasionally to nitrogen, and has a strong chemical affinity to phosphate, with which it forms crystals which are similar to quartz and silicic acid.

Measurement of Al in any complex matrix such as blood or tissue is quite difficult and presents another challenge to the study of the metal's role in metabolism. All analytic results must be assessed carefully. Berlyne and Adler (1985) reflect the uncertainties in the literature. They advise that all published serum Al values should be viewed with skepticism and that efforts should be made to improve the accuracy of Al assay in biologic fluids and tissues. A detailed description of analytic methods is provided in a previous document (see appendix 1: L.F. Smith and C. Archer: Background Paper on Aluminum: Origins, Uses, Biology and Health Issues, January, 1989).

Certain elements share chemical characteristics. Al is among such a group which also includes iron (Fe), chromium (Cr), gallium (Ga), yttrium (Y), scandium (Sc) and zirconium (Z). Al has no long-lived radioisotope which would enable tracer studies while Ga and Fe do. Therefore, a study of the metabolism of Fe and Ga in animals has contributed to our knowledge of the behaviour of Al.

3. ALUMINUM BALANCE (INTAKE, UPTAKE, DISTRIBUTION AND EXCRETION)

3.1 GENERAL

The metabolism of a substance in the body can be studied in various ways: by time-trend analysis of normal and unusually exposed human populations; by balance studies in humans and laboratory animals; and by controlled human and animal multi-route exposure studies. These studies become easier to carry out with a long-lived, traceable isotope; none exists for Al. In general, the information needed is intake, uptake, distribution and excretion. From these parameters, the build up of the substance in the body (deposition) and turnover can be measured or calculated.

There is ample opportunity for Al to be absorbed and retained in the human body given its abundance in nature. Therefore, normal body content of Al should be a reflection of its retention and lifetime accumulation in the body.

Total body Al from dietary sources does not tend to accumulate with age (Alfrey in Gitelman, 1989). Several reports of Al content in normal men point consistently to a total human body content of Al from 30 to 50 mg (or about 1 day's intake from normal dietary sources), a fact which supports the contention that there is little to no tendency towards retention in the body. Half of the body Al rests in the skeleton and one quarter in the lungs. As the lung burden may be primarily from inhalation of environmental dusts, the total body retention from absorption is indeed quite small. One

must hypothesize that selective deposition and accumulation at the subcellular level without any significant increase in the corresponding tissue concentration or in total body Al content must occur in order to explain its role in disease. Since excretion of absorbed Al is almost entirely through the kidneys, dialysis patients provide a unique opportunity to study Al balance and toxicity.

3.2 INTAKE

The quantity of Al in the normal diet varies considerably. Normal human dietary intake averages about 40 mg daily. This daily intake can be increased by Al-containing medications (200-mg Al per day for antacids) and by the injection of vaccines which are adsorbed to aluminum hydroxide (1.5 mg Al per dose), although it is not clear that Al from vaccines is distributed throughout the body. Aluminum acetylsalicylate (aspirin-Al) contains about 12% - 17% Al oxide by weight in each therapeutic dose (Hem and White in Gitelman, 1989).

3.3 UPTAKE

3.3.1 UPTAKE FROM THE GASTROINTESTINAL (GI) TRACT

Al uptake from the GI tract in humans can be studied by measuring intake of dietary Al and output into the urine and feces. Studies in normal and renal-impaired men (reviews by Skalsky and Carchman of: Tipton, 1976; Clarkson, 1972; Cam, 1976; Gorsky, 1979; and

Greger, 1983) provide a guarded conclusion that there is an approximate relationship between the amount ingested (i.e. swallowed) and the amount absorbed as calculated from fecal excretion of Al. Absorption into the blood stream (and excretion through the kidneys) is inferred by subtraction. Their review supports a very small, almost immeasurable, absorption through the gut when amounts below 225 mg/day are ingested and a higher absorption above this ingestion level. These and other data support a model of Al absorption that involves an active transport mechanism across the intestinal wall at low levels of Al intake and passive transport mechanism at higher levels of intake (Skalsky and Carchman, 1983).

Cellular contents, generally polar, cannot leave the cell and unwanted substances from the environment cannot get in. Polar substances, such as Al, are not able to cross the cell membrane unaided. The membrane serves as a gate, allowing substances to go across a concentration gradient, from high to low, called mediated passive transport. Active transport is the carriage of a solute particle against a concentration gradient. Active transport implies the action of a carrier molecule to ease the transport and the consumption of metabolic energy in so doing. It is by far the most important transport mechanism in the body. Passive and active transport differ in turn, from osmosis which is the passage of water across a concentration gradient of a solute, a process driven by osmotic pressure.

The mechanism for transferring Al across the intestinal mucosa is inferred from the knowledge of the chemical behaviour of Fe, a metal similar to Al whose transport mechanism is known. The site in the intestine where Al is absorbed is not known. However, iron binding sites occur primarily in the duodenum, so it is possible then, that Al is also absorbed there. Transferrin (the iron-protein--a beta globulin) in the intestinal mucosal cells binds and actively carries Fe to the blood stream. Al competes with iron for transferrin binding sites and may compete with the binding sites of the active transport proteins of other metals. However, as the concentration of Al increases in the intestinal tract, the available transferrin binding sites are filled, but, the probability of its existing as a polymer (a very large molecule formed by the chemical bonding of similar molecular units) or as a precipitated hydroxide also increases (Ganrot, 1986) thus decreasing its availability for transport. It is hypothesized that Al absorption at these higher levels, therefore, takes place through other mechanisms, possibly passive transport.

Urinary excretion is the best indicator of absorption. The lowest reported range for urine Al concentration is 20 to 50 ug/day (or 500 to 1000 nanomoles/day) which can also be taken as the normal range (Ganrot, 1986). Assuming a daily intake of 20 mg and no retention, a 24 hour urinary excretion of 20 - 50 ug of Al reflects an absorption fraction of 0.1 to 0.3%. From other data on the absorption of Al in antacids (in the form of aluminum hydroxide) at

an ingestion level of 2.2 gm daily, the observed upper level of daily urinary excretion of 300 ug would imply an absorption fraction of about 0.01%. Al absorption depends to some extent on the substances to which it can be attached (called ligands), form a non-polar complex, and gain access to the blood through the cell. Oral Al glycinate, for example, produces double the urinary excretion of Al hydroxide from which one can infer that there was at least double the absorption (Ganrot, 1986).

A ligand of particular recent interest is maltol, a sugar-based additive in today's processed foods. Maltol binds Fe and Ga, and Al. When maltol binds Fe, a neutral (uncharged) molecule is produced which is able to cross the cell membrane. Barrand et al. (1987) found that iron uptake was significantly enhanced in iron-deficient rats at low levels of iron-maltol intake but not at high levels. Farrar et al. (1988) demonstrated in a Ga-maltol rat model that, in fasted rats, maltol enhances the absorption of Ga as compared to Ga alone. The tissue distribution, however, was unchanged. In fed animals, there was no difference in the absorption between Ga alone or Ga-maltol. The authors propose the following explanation of their findings. Normal food constituents prevent the formation of the metal-maltol ligand by binding maltol. The authors further conclude that "...any aluminium-maltol complex that is formed as a result of the simultaneous ingestion of these compounds should not be absorbed over and above the normal levels for aluminium transport (average intake is 5 mg Al/kg; Bertholf et

al., 1988). Although aluminium is acknowledged to be a neurotoxin (sic, toxic when introduced by directly into the brain), this study suggests that aluminium-maltol complex in fed animals may not pose an increased neurotoxic threat over aluminium alone as was suggested by earlier studies (Finnegan et al., 1986, 1987)".

Recent work of Kruck et al. challenges the findings above. They demonstrated that Al-maltol complexes enter the bloodstream of fasted rabbits after a single oral dose. Serum Al remained elevated after three days and there was a sustained increase in urinary excretion of Al for up to 30 days. These observations support a model of the existence of an extravascular distribution of Al-maltol from which it is then slowly released. Compartments to which Al-maltol distributes may include brain cells (T.P.A. Kruck, 1989, personal communication). In support of this, rabbits treated with daily oral Al-maltolate, then sacrificed after 11 days of normal feeding demonstrated a three-fold increase in brain intranuclear aluminum content (Kruck and Crapper McLachlan, 1989, in press). The authors conclude that Al-maltolate is capable of entering the brain cell nuclear compartment from oral dosing. This work has not yet received widespread scientific review.

Other conditions which may affect the absorption of Al from the gut are parathyroid hormone status (parathormone promotes absorption) (Smith and Faugere, 1986), phosphate co-ingestion (phosphate diminishes absorption by binding and precipitating Al) and iron

balance (iron deficiency increases Al absorption by allowing more transferrin, the iron-binding beta globulin, to be available).

3.3.2 UPTAKE FROM THE SKIN

Aluminum chlorohydrate, an antiperspirant, is not absorbed beyond the outside layer of the skin. Al gets trapped in the sweat glands, dissolved by sweat, precipitated within as Al hydroxide but is not absorbed systemically (Hem and White in Gitelman, 1989).

Alfrey states that there is no evidence that Al can be absorbed systemically through the skin, even with high exposure (Alfrey in Gitelman, 1989). Several preparations containing Al make use of its astringent qualities: Burrow's solution (Al acetate) as a topical wet dressing and aluminum oxide cream for acne.

A single reference in the literature describes a case of atypical motor neuron disease in a man who had used a 38% Al oxide cream on the facial skin for many years (Ross et al., 1986). The investigators claim to have demonstrated systemic Al overload by the use of DFO challenge, an investigational protocol in people with normal kidney function (Crapper McLachlan et al., 1985). The man received DFO for a period of six months, maintained increased Al in urine for a similar period, and had concurrent slowing of progression of his disease and some improvement two years later. This is the only case study which refers to systemic absorption of Al through the skin by the use of a carrier which can transport it across the skin cell membrane much as a ligand may do in the gut

(Kruck and Crapper McLachlan, 1989). Ross et al. describe neither the carrier nor the intactness of the patient's skin.

3.3.3 UPTAKE FROM THE LUNGS

Al from welding fumes is absorbed through the lungs. Urinary and plasma levels of Al rise after exposure to Al welding fumes and decrease when exposure stops (Mussi, 1984; Sjogren, 1983, 1988). No evidence to date has emerged, however, that dusts of oxides of Al as produced in mining and manufacturing processes are taken up systemically by this route. Metallic Al dust used as prophylaxis against silicosis has not been noted to be absorbed systemically through the lungs in humans. Dust particles may be coughed up, swallowed, and then possibly absorbed through the gut.

Morgan and Dinman (1989) have reviewed the literature extensively back to the early 1930s when there was considerable concern about the occurrence of silicosis in certain industries. The authors cite several reports which support the hypothesis that Al oxide is harmless with regard to lung fibrosis (Meiklejohn, 1963; Sutherland et al., 1937; cited by Morgan and Dinman in Gitelman, 1989). No reference, however, is provided concerning its uptake into the bloodstream.

Animal studies have attempted to assess the value of the inhalation of Al powder in the prevention of silicosis. These experiments do not include a study of its systemic uptake from the lung.

3.4 TRANSPORT, TISSUE DISTRIBUTION AND EXCRETION

Ganrot (1986) has reviewed extensively the literature on the transport and availability of Al in plasma. The Al ion (Al^{+3}) is bound to transferrin (60 - 70%) and albumin (10 - 20%) in plasma (Trapp, 1983). Some percentage of Al, from 30 to 50%, is ultrafilterable (i.e. not protein-bound, and therefore of a small enough size for excretion by the kidneys). Under normal conditions in the blood, ultrafilterable Al is probably bound to phosphate or to citrate once the availability of transferrin binding sites is exceeded (Alfrey in Gitelman, 1989). The transferrin binding capacity is exceeded in vitro by the addition of Al. In vivo, only about 35% of transferrin sites are occupied by Fe. In normal circumstances, Al levels are relatively low in comparison to available transferrin sites. However, the proportions of protein-bound and ultrafilterable Al are basically unknown.

Some studies on plasma binding carried out in dialysis patients demonstrate that plasma binding increases as the concentration of Al decreases. This suggests that, when there has been a large Al exposure producing high blood serum Al levels (as in reported cases of patients in renal failure on large doses of Al-containing antacids or on dialysis with Al-bearing water), the normal capacity of the plasma to bind Al (into large protein molecules) may be exceeded and the remainder (being smaller molecules, such as Al phosphates or citrates) then is ultrafilterable. The

ultrafilterable fraction may be available for tissue deposition as well as for excretion by the kidney.

The lung has the highest concentration of Al, probably around 20 mg/kg wet weight (Ganrot, 1986). Bone has a concentration of about 5-10 mg/kg. A larger proportion of total body Al rests in bone as bone mass is greater than lung mass. Al concentration in other tissues is generally considerably lower than lung and bone.

The brain concentrations have been fairly consistent at about 0.25 to 0.75 mg/kg (ppm) wet weight with different concentrations in different areas of the brain, gray matter being higher than white matter. Very few data are found in the literature on any age differences of Al concentration in either plasma or body tissues. Increases with age have been reported for all tissues, although the amount of information is limited. It is proposed that some accumulation may take place at a subcellular level without any significant increase in the corresponding tissue concentration (Ganrot, 1986).

According to Alfrey, bone is the most reliable (and reasonably available) tissue for studying body Al (Alfrey in Gitelman, 1989). Plasma (or serum) Al reflects conditions of transport in the body resulting from immediate body loading and is not indicative of body burden (Alfrey in Gitelman, 1989).

Ganrot (1986) refers to experiments on dogs administered Al intravenously. The animals showed a plasma elimination half-time of 30 minutes (i.e. serum concentrations dropped by 50% in 30 minutes) and whole body clearance of one third the dose within 2 hours (i.e. 33% of the total injected Al was excreted in urine within two hours). The half-life of Al in plasma as calculated from human experimental data of similar metals is roughly 4 hours, a value for Al supported by animal experiments (Ganrot, 1986).

Studies of men with occupational exposure to Al fumes determined that the biologic half-life of Al as measured by urine excretion is about nine days in workers exposed less than 1 year and increases to about six months after 10 years exposure (Sjogren et al., 1988). This supports the contention that some retention of Al occurs in some body compartment for a limited period after continuous exposure to aluminum-bearing fumes or dust for longer than a year.

However, most investigators contend that there is no retention of Al from nutritional sources in the healthy human with normal excretion (i.e. with normally functioning kidneys). Against this statement is the evidence that Al concentration in specific organs in older adults is higher than in the newborn (e.g. 0.7 mg/kg vs 0.2 mg/kg wet weight in the brain) so that very limited accumulation probably occurs. Retention of Al in the lungs results primarily from inhalation of largely insoluble salts from the

environment, not from uptake from the gastrointestinal tract. Lung retention has little metabolic interest.

Brain levels of about 3 mg/kg wet weight are associated with clinical manifestations of toxicity in DES. Normal brain levels range from 0.25 to 0.75 mg/kg wet weight, about three to tenfold less. In normal people, if brain Al does accumulate slowly and is not eliminated from the brain, Canrot calculates that a toxic level (of about 3 mg/kg wet weight as in DES) would result after 100 to 150 years. The mechanisms whereby Al gains access to brain cells across the blood-brain barrier are not known. They may be different in DES than in other diseases with reported elevated Al level in brain such as SDAT or ALS-PD.

3.5 BIOLOGIC MONITORING AND MEDICAL SURVEILLANCE

Biologic monitoring of subjects exposed to any substance should be supported by information on its metabolism (intake, uptake, distribution, excretion), its critical effects, accurate measures of dose, the relationship between exposure level and measured uptake or dose, and the relationship between dose and adverse health effects to be measured (Alessio and Bertelli, 1981).

In a joint meeting of representatives from the European Economic Community (EEC), the National Institute of Occupational Safety and Health (NIOSH), and the Occupational Health and Safety Administration (OSHA), biologic monitoring was defined as "a

systematic or repetitive health related activity designed to lead, if necessary, to corrective action" (Savory and Berlin, 1983). In addition, the same meeting defined biologic monitoring as "measurement and assessment of agents or of their metabolites either in tissues, secretta, excreta, expired air, or any combination of those to evaluate exposure and health risk, compared to an appropriate reference" [emphasis supplied].

Aitio (1988) echoes the above considerations and suggests that biologic monitoring requires that four conditions be met:

1. The substance and or its metabolites are present in some tissue, body fluid, or excretion suitable for sampling;
2. Valid and practical methods of analysis and sampling are available;
3. The measurement strategy is adequate (the samples are representative); and
4. The result can be interpreted.

Therefore, the feasibility of biologic monitoring is determined by two kinds of considerations:

1. a knowledge of the toxicology and kinetics of the substance, and
2. practical aspects (Aitio, 1988).

The World Health Organization has made recommendations regarding the medical surveillance of workers in industry and agriculture

(WHO, 1975). They echo the authors above as well. Assumptions are made that:

1. exposure to a specific hazardous work factor has been established;
2. sufficiently specific biological indices for exposure and effect are available;
3. permissible levels in biological specimens have been agreed upon;
4. diagnostic procedures to be applied in the field are available.

The WHO document also recommends (among many recommendations made) that biological indices should be measured in all workers before they are exposed or that measures should be obtained from a control group comparable in age, sex, sociocultural and economic status; that the measurements should be performed on the same day of the week at the end of the working day (WHO, 1975). A later WHO report (Early Detection of Occupational Disease, WHO 1986) echoes the previous publications stressing the need for knowledge of the kinetics, metabolism, and sensitivity of analytic methods of body fluids as a minimum before any monitoring program is in place.

Much information has been recently published on the metabolism of Al. However, present knowledge on the metabolism of Al does not meet the prerequisites to support the use of serum or plasma Al as a tool for monitoring occupational exposure or for early diagnosis of disease (screening) with the possibility of treatment or of

prevention of more severe disease (secondary prevention) in persons with normal renal function. On the other hand, monitoring of Al in persons on dialysis is useful for therapeutic reasons (viz. early diagnosis and treatment of bone disease and prevention of the dialysis encephalopathy syndrome discussed below).

Investigators have collected data to evaluate the relationship of measured levels of Al in blood, urine and bone to body burden and to exposure in the normal and the renal-impaired. Plasma and serum Al have been used as an indirect method of either Al exposure or body burden. However, although readily accessible, serum or plasma Al is not a reliable quantitative indicator of either the exposure or body burden in normal persons (Alfrey in Gitelman, 1989). Urinary Al reflects daily uptake from all routes. Consequently, the urine may be the body fluid of choice to monitor Al exposure in occupations provided that other sources of Al are known. Urinary Al in those unexposed beyond the food chain does not usually exceed 15 ug/day (535 nmol/day) (Aitio, 1988).

Several investigators have reported normal values of Al in serum. The Ontario Ministry of Health surveyed serum and urine Al in 63 laboratory staff presumably unexposed beyond the food chain. The median concentration of serum Al was between 25 and 50 nmol/L; the maximum concentration found was 200 nmol/L. Daily urinary excretion in the same group was 600 nmols (Dr. Helen Demshar, personal communication, 1989). The University Hospital laboratory

in London, Ontario reports 370 nmol/L as its upper limit of normal (Leung and Henderson, 1982). Versieck and Cornelis (1989) summarize the literature on normal Al values and give 10 ng/ml (10 ug/L or 370 nmol/L) as the upper limit of normal using standard analytic techniques of graphite furnace atomic absorption spectrophotometry (GFAAS) or inductively coupled plasma atomic emission spectrophotometry (ICP-AES). Wilhelm et al. reported a range of serum Al of 37 to 233 nmol/L (or 1-6.3 ug/L) in a control group of 50 persons (Wilhelm et al., 1989).

Serum Al levels in renal failure patients may rise to very high levels, in the range of 7400 nmol/L. Persistently elevated serum Al to 7400 nmol/L in dialysis patients is associated with the encephalopathy syndrome. Therefore, serum Al guideline levels have been developed for the purpose of medical surveillance of patients undergoing hemodialysis in order to guide treatment. Wilhelm et al. studied both dialysis patients and controls with the objective of relating Al exposure to aluminum in serum, bone and hair. Hair was not found to be a useful monitoring tool. Plasma Al concentrations did not correlate well with bone Al levels (correlation coefficient: 0.350) or with daily intake (correlation coefficient: 0.121). Stainable Al in bone mass seemed to be the best measure of excess Al body burden. The results of Wilhelm et al. "...clearly indicate that plasma aluminum levels do not reflect a patient's aluminum body burden. However, the aluminum concentrations in plasma reflected the elevated aluminum exposure

from oral intake of phosphate binding drugs and contamination of the dialysis fluid" (Wilhelm et al., 1989). Smith et al. demonstrated similarly that aluminum-related bone disease, which occurs in 50% or more of dialysis patients who develop dementia, can only be diagnosed by bone biopsy (Smith et al., 1986).

Chelating agents bind metal ions and therefore are used in chemotherapeutic treatments for metal poisoning. The chelating agent desferrioxamine (also known as: deferoxamine, Desferal^R (CIBA-Geigy) or DFO) has been used exclusively for iron removal in various conditions of iron overload and in iron poisoning. It is administered by intravenous infusion or intramuscular injection. DFO has been used successfully in the treatment of the osteodystrophy (bone disease) and encephalopathy caused by Al overload in hemodialysis patients. Currently, DFO is also used prophylactically in selected hemodialysis patients to prevent Al accumulation (Savory, 1986).

In patients with renal failure, a rise in plasma Al following a dose of DFO reflects the size of the chelatable Al pool and correlates with bone Al concentration (Alfrey in Gitelman, 1989). Malluche and Faugere's work demonstrates that a rise of 20% above baseline serum Al after DFO challenge in renal failure patients is suggestive, though not diagnostic, of high bone Al. Therefore, such a result requires bone biopsy to confirm the presence of stainable Al (Malluche and Faugere, 1988). A result below 20% is

diagnostic of no stainable Al in bone. High bone Al concentrations reflected as stainable Al relate well to osteodystrophy and to encephalopathy. Therefore, the DFO challenge in renal failure patients provides a useful, relatively non-invasive guide for treatment of severe diseases - osteodystrophy and encephalopathy.

The following criteria have been recommended for the management of dialysis patients (Savory et al., 1983):

- serum aluminum concentrations should never exceed 200 ug/L (7400 nmol/L);
- concentrations over 100 ug/L (3700 nmoles/L) should be viewed with concern and require careful monitoring;
- concentrations from 60 to 100 ug/L (2220 nmol/L to 3700 nmol/L) appear to cause no problems to the patient in the short term;
- serum aluminum should be monitored in all dialysis patients four to six times per year.

In individuals with normal renal function the DFO may be cleared by the kidneys too quickly (since its half life is 90 minutes) for it to have reached the target tissue (bone) with most of the Al stores (Alfrey in Gitelman, 1989). Its usefulness as a diagnostic tool is thus limited.

DFO is currently being tested as a diagnostic and therapeutic tool in patients with normal renal function and several types of neurological disorders. Toronto investigators are carrying out a

clinical trial to test the therapeutic benefits of DFO in patients with demonstrated Alzheimer's disease (Crapper McLachlan et al., 1985). The same team of investigators previously reported a patient with atypical motor neuron disease and a history of application of a 38% Al oxide cream for 25 years (Ross et al., 1986). This patient demonstrated a persistent increased excretion of Al in urine after treatment with DFO by the protocol used by Crapper McLachlan and colleagues as compared to a control (the patient's brother). The authors claim that this patient's disease has not progressed and that after a two year follow-up, the patient has demonstrated improvement in muscle strength (Kruck and Crapper McLachlan, 1989).

Although the Toronto clinical trial still continues, the investigators have reported preliminary findings after the brains of six cases with SDAT (Alzheimer's disease) who died from other causes became available (Kruck et al., in Iqbal et al., eds., 1989, in press). Four of these six cases had been treated with DFO while the other two had not. The four treated cases were separated into two groups: the long term group (defined as patients who had been treated with DFO over 3 months); and the short term group (defined as patients who had less than 7 DFO injections). The investigators reported lower levels of brain Al in the long term treatment group. They conclude: "These findings demonstrate that the [DFO] treatment employed has indeed caused a decrease in brain aluminum levels in patients with AD." (Kruck et al., in Iqbal et

al., eds., 1989, in press). However, this conclusion could only hold if the Al brain levels in each of the long and short term treatment groups were known before DFO application; and if the reduction in brain Al were significantly greater in the long term group as compared with the short term group.

3.6 SUMMARY

- Aluminum (Al) does not accumulate in the normal human body. This suggests that its normal uptake and excretion are balanced. Total adult body Al is about 30 - 50 mg, or about one day's dietary intake.
- Al concentration is highest in lung tissue, followed by bone. However, 50% of the total body content of Al is in the bone mass and 25% is in lung.
- Al levels in lung tissue may increase with age because of inhalation (of dust) or because of absorption (and systemic deposition). However, inhalation of dust is more likely.
- Brain levels may increase with age although the mechanisms of deposition and its role in disease are not well understood.
- The lungs absorb Al from welding fumes. However, information on Al exposure and absorbed levels is limited. Evidence suggests that the body retains Al from welding fumes for relatively short periods of time (ranging from days to months) depending on length of exposure.
- The gastrointestinal tract does not absorb Al readily. Al is probably actively transported across the gut mucosa by the

iron transport beta globulin, transferrin. The amount of Al absorption in the gut depends on its concentration there in relation to food components: on its chemical structure (viz. polymer, complex, combined with ligands: glycinate, maltolate, citrate, phosphate, etc.); and on the physiologic state of the organism (hormone status, diet, iron deficiency, fasting state, etc.).

Since Al absorption cannot be directly assessed, the model for Al-maltol absorption is based on knowledge of Fe and Ga transport since these metals are similar in behaviour to Al:

- The Fe model in rats has demonstrated that iron overload (from too much ingestion) does not occur in iron-deficient animals. However, iron absorption from iron-maltol is enhanced in starved but not in fed animals;
- The Ga absorption model in rats demonstrates that animals are not likely to absorb Al under conditions of normal food intake because Al does not preferentially associate with maltol in the presence of food constituents.
- Recent work suggests that Al-maltol can reach the brain of rabbits on a normal diet treated with daily oral doses of Al maltolate. The source of maltol for humans is exclusively from processed food.

Transferrin, albumin and non-protein plasma elements transport Al in the blood. The half-life of Al injected into dogs is 30 minutes, and the 24 hour whole body excretion fraction

determined from urine is 30%. The theoretical half-life in plasma is estimated at roughly 4 hours.

Plasma and serum Al are accessible but not reliable measures of exposure or body burden in persons with normal renal function. Urinary Al reflects uptake from all routes and may be a useful monitoring tool of current uptake when all sources of exposure are known and controlled.

There is limited, non-systemic absorption of Al from antiperspirants into sweat glands. However, there is one case report of dermal exposure to Al oxide cream and persistent elevated excretion of Al during treatment with DFO.

In persons with kidney failure, serum Al has a low, but positive correlation with bone Al and is used as an indicator for body burden when accompanied by DFO challenge and bone biopsy. If stainable Al is present in bone, then treatment for Al overload may be initiated. Currently, dialysis centers use specific guidelines for this treatment.

The relationship between the body burden of Al and urinary aluminum excretion after DFO challenge in persons with normal kidney function is still under investigation.

4. ALUMINUM RELATED HEALTH EFFECTS

4.0 GENERAL

Hazardous occupational exposures generally arise out of the mining, smelting and refining operations of Al and its ores. The hazards generally arise from the processes and not specifically from Al. The open mining of bauxite gives rise to a few reports in the literature of "bauxite" lung, which Dinman attributes to the presence of crystalline silica (Dinman, 1983). The Soderberg and prebake electrolytic reduction processes may emit large amounts of fluoride dust and alumina as well as sulfur dioxide, oxides of carbon and hydrogen fluoride. Exposures to these are fairly well controlled by ventilation and monitoring of the work environment and of workers (urinary fluorides). Excessive exposure to fluoride results in fluorosis, a condition of the bones and teeth, rendering them brittle. The fluorosis that was once the major risk to health in aluminum reduction plants has been replaced by the effects from inhalation exposure to polycyclic aromatics from pitch fumes and particulates. This is especially so in Soderberg process plants. Such exposures are associated with lung cancer among workers employed in Soderberg-type reduction cell smelters (Stokinger, 1981). Workers in contact with pitch fumes may develop a skin condition associated with irritation and itching on exposure to sunlight. Workers involved in the manufacture of the electrodes are exposed to pitch dust and carbon and can develop conditions indistinguishable from coalworkers' pneumoconiosis. Potroom workers are at risk of potroom asthma which results in sustained

respiratory dysfunction after removal from work (Wergeland et al., 1987). An increased incidence of ischemic heart disease has been noted in reduction plant workers, especially potroom workers, but no occupational causative factor has been identified (Theriault et al., 1988). Fumes from soldering operations can result in a delayed-type asthma. The inert-gas tungsten-arc welding process can protect from this but can lead to other respiratory symptoms if ozone exposure is not well controlled.

4.1 THE SKIN

Skin irritation can occur from repeated contact of the skin with soluble aluminum salts. Early twentieth century publications refer to an anesthetic condition of the fingers (acroanaesthesia) following long contact with alum (Stokinger in Patty, 1981). Contact sensitivity to Al resulting from intradermal exposure to Al-precipitated pollen injections was reported by Clemmensen and Knudsen (1980). Hall (1944) reported an array of occupational contact dermatitides in aircraft workers, for which Al was only rarely the cause. Fischer and Rystedt (1982) published a case report of a hard metal worker who developed Al skin sensitivity from the use of Al containing antiperspirants. None of these conditions proved incapacitating and the causal factor was generally easily avoidable.

Skin telangiectases (a spot formed by a dilated capillary or small artery, usually under the skin) occur in primary aluminum

production workers. The group at risk is the potroom workers in the Soderberg electrolysis process where exposure to various aromatic hydrocarbons occurs. The telangiectases observed in potroom workers, however, have a different pathologic picture from the known four types (Theriault et al., 1980) and carry no particular health risk (Theriault et al., 1984). In Quebec, skin telangiectases are compensated as an occupational disease on the basis of "aesthetic prejudice" (Rossignol and Theriault, 1988).

4.2 THE LUNG

The lungs are continually exposed to environmental Al usually in the form of silicate dusts. The review literature contains many references that Al compounds do not produce lung fibrosis except in special circumstances. The reports which follow support this. Conditions other than fibrosis have been noted rarely.

4.2.1 CASE REPORTS OF LUNG EFFECTS

1. PULMONARY FIBROSIS (including "ALUMINOSIS")

The first report in the English language literature of occupational disease specifically due to Al exposure came from England in 1959 (McLaughlin et al., 1962). This unique report described a new clinical syndrome in a young man working in the pyrotechnics industry as a ball mill operator (smashing aluminum flake to a powder) who developed rapidly progressive encephalopathy with seizures, resulting in death. This industry had manufactured the

powder used as an explosive in shells during and after WW II and currently manufactured pyro for fireworks. This single case was found to be the index of an unusual cluster of diseased workers in the same factory investigated and reported by Mitchell (Mitchell et al., 1961). The co-workers of this index case demonstrated, not encephalopathy, but pulmonary fibrosis. On review, the chest x-ray of the deceased demonstrated some pulmonary changes compatible with fibrosis but he had not experienced any respiratory symptoms prior to his final illness. The post mortem examination revealed pulmonary fibrosis and the presence of 20 um Al particles throughout the lung.

Of his 53 co-workers, 48 volunteered for chest x-rays and 23 for clinical examination with lung function tests. Thirteen of the 23 had worked in the aluminum powder room and were considered "maximally" exposed. These had a higher rate of "pulmonary abnormalities" (6 of 13) as compared to the lesser exposed (2 of 12) and least exposed (1 of 28). No other case of fibrosis was found and none had neurological signs or symptoms. McLaughlin suggests that the pulmonary fibrosis is "undoubtedly" related to Al dust. (McLaughlin et al., 1962).

Mitchell, however, learned that the worker who replaced the ball mill operator who developed encephalopathy and fibrosis also died. He then investigated 27 of 30 former workers of this plant and found that six had evidence of pulmonary fibrosis, including two

who died as a result of the fibrosis. Mitchell concluded that "pulmonary fibrosis was caused by dust inhaled at work and that the component responsible was finely divided aluminium" (Mitchell et al., 1961).

McLaughlin stated that the Al dust to which the present case had been exposed was coated in animal fat (stearic acid). However, there had been previous exposure to Al powder coated in mineral oil (Mitchell et. al 1961; Dinman, 1987). The move to mineral oil coating represented a refinement in the armament industry since it enabled an increased concentration of Al powder in shells, and hence an increased explosive power.

Jordan (1961) reported a case of a female fireworks worker who presented in 1955 with respiratory symptoms and evidence of pulmonary fibrosis. She had worked packing Al powder with potassium perchlorate into fireworks cartridges for five years in the early fifties. Her clinical findings were similar to those reported by Mitchell (Jordan, 1961).

No case of fibrosis was reported from the fireworks industry subsequently. In 1987, Dinman re-examined the history of Al and pulmonary fibrosis. He relates the reports from Germany in the late forties describing the occurrence of a progressive pulmonary fibrosis in the German pyrotechnics industry. These reports stressed the occurrence of this new occupational disease as early

as 1939 concurrently with a change in the oil used to coat the highly reactive fine Al powder. The change from stearic acid to mineral oil occurred between 1938 and 1945 (Goralewski, 1947 in Dinman, 1987). Prior to 1938, no case of "aluminosis" had been reported despite wide experience in pyrotechnics. In the United States, only stearic acid was used and no convincing case of "aluminosis" could be found in the literature (Morgan and Dinman in Gitelman, 1988; Morgan, 1989b).

England reintroduced the use of mineral oil to coat pyro powder in the early 1950s, a period from which came the workers studied by Mitchell, McLaughlin and Jordan. Dinman reports that about 1955, the lubricant was again changed to stearic acid. The cases of fibrosis were drawn from a period when stearic acid was either not used, or used blended with mineral oil.

In brief, the disease "aluminosis" or pulmonary fibrosis due to exposure to finely divided aluminum (pyro) powder is a unique syndrome of historical interest related to exposure to the highly reactive pyro powder during a period when it was coated with a non-polar mineral oil. Mineral oil readily dissociates from the powder in a water medium allowing the pure aluminum to react with tissues. This reaction is known to be highly exothermic (producing heat) and capable of inducing tissue damage. This reaction undoubtedly contributes to the pulmonary pathology.

The causal link of free Al to the fibrosis in this occupational cluster is not disputed at present. There is convincing evidence that with the use of animal fat to coat the Al powder, no disease occurs and with the use of mineral oil, disease occurs. There is support for the association in both the cross-sectional study carried out by McLaughlin in the co-workers of the index case with encephalopathy (McLaughlin et al., 1962), the historical cohort study carried out by Mitchell in the same factory (Mitchell et al., 1961), a case report by Jordan (Jordan, 1961) and by reports from similar work place conditions in Germany where the association was first noted in 1939 (Goralewski, 1947) and in Sweden (Jager, 1941).

Pulmonary fibrosis was reported in an aluminum polisher who also developed bronchial carcinoma (De Vuyst et al., 1986). This case report describes a 61 year old man who worked in an environment with aluminum dust but not aluminum powder, bauxite, or welding fumes. He had worked as a metal polisher for 12 years followed by an interruption of 12 years, and then metal polishing for 12 years. In the latter period he polished aluminum with abrasives primarily, but also stainless steel, and occasionally plated chromium and nickel. He had been a heavy cigarette smoker. He presented with a 10 year history of shortness of breath and non-productive cough increasing to the point that he had to stop working 5 years previously. He was found to have a bronchial carcinoma with bone metastases.

Post mortem examination confirmed the presence of diffuse interstitial fibrosis and honey-combing (emphysema), as well as the bronchial carcinoma but no silicotic nodules or sarcoid granulomas. Mineralogical analysis of lung tissue revealed that Al represented 1/3 of all particles and silicium 1/4. The authors state that this is compatible with metallic Al, Al_2O_3 , silica and carborundum. There were other dust components also present: iron oxides, titanium dioxide, zircon, chromite, Badderleyite and stainless steel.

The authors state that this worker had an occupational pneumoconiosis and that the causal role of all dusts could not be ruled out. They, however, believe that the abundance of Al in the lung tissue supports an etiologic role for this metal. However, the pattern of fibrosis in this patient is not similar to that seen in aluminum lung and the presence of Al particles in the lung does not indicate that the Al led to the fibrosis (Morgan, 1989b).

2. PULMONARY ALVEOLAR PROTEINOSIS AND AL DUST

Pulmonary alveolar proteinosis (PAP) is a disease of unknown cause which appears in association with exposure to fine silica dust in humans. PAP was first described in 1958 and is characterized by the accumulation of a lipoprotein exudate similar to surfactant in the alveoli. PAP may occur "spontaneously" upon exposure to a variety of inorganic dusts (Morgan and Dinman in Citelman, 1989). In this case, the exposure is purported to be Al dust.

Miller described the case of a 44 year old Al rail grinder working in a "dusty" environment with no protective mask. The disease was characterized clinically by cough and shortness of breath on exertion, weight loss, restrictive lung disease with impaired diffusion capacity. Biopsy showed alveolar proteinosis and the presence of 1 μ m Al particles, alone and in clumps, as well as iron, kaolinite and mica. The Al particles were of varying size but all were microspheres. The author holds that this case represents an example of PAP induced by inhalation of aluminum particles (Miller et al., 1984).

Morgan and Dinman took a special interest in this case report by Miller and related it to the 1982 case report by Herbert et al. below. They challenged the findings of Miller and hypothesized that the coarse Al flakes and particles likely to have been produced by a grinder would not have been respirable, although occasionally respirable particles can be produced if the grinding wheel is turning quickly (Morgan and Dinman in Gitelman, 1989). The fine Al powder possibly could have been in the form of a liquid aerosol, much as a fume, which would be capable of producing PAP but not fibrosis. These fine liquid aerosol particles could have cooled to respirable spherical forms. The possibility that the grinder was exposed to fumes from neighboring workers could not be excluded (Morgan, 1989a).

3. DESQUAMATIVE INTERSTITIAL PNEUMONIA IN AN ALUMINUM WELDER

Herbert et al. describe the case of a 35 year old welder who developed a rather rare pulmonary condition, desquamative interstitial pneumonia (DIP). His usual exposures were to iron and magnesium, but he wore a protective mask. This 16-year veteran welder developed fairly rapid progressive pulmonary symptoms. Lung biopsy demonstrated a desquamative pneumonia with Al particles present in the tissues surrounding the bronchi and the blood vessels. (A desquamative pneumonia demonstrates the presence of cells, usually macrophages, in the air sacs and in the spaces between them.) The authors suspected that the presence of Al particles may be the cause of this worker's disease. However, they commented on the occurrence of this picture in the lung as a response to a variety of other dust insults (iron, talc, silica, graphite, asbestos and other dusts) (Herbert et al., 1982).

4. PULMONARY GRANULOMATOSIS

The literature presents several reports of this condition in workers with exposure at some time to Al (Chen et al., 1978; De Vuyst et al., 1987; Fernandez, 1986). Chen described a worker who had been a welder in the aircraft industry for 5 years. His work history included the following: cedar saw mill (5 years), rock crushing (2 years), aircraft industry welder (5 years), fiberglass resins (3 years). His chest x-ray was normal when he left the aircraft industry but he developed x-ray changes (diffuse interstitial infiltrate pattern) six years later while he was

working with fiberglass resins. The diagnosis of pulmonary granulomatosis was confirmed by lung biopsy. Intracellular crystals containing Al were found.

De Vuyst reported a chemist working for eight years in a dusty environment with many metal dust exposures including Al dust. He presented with shortness of breath on exertion and cough of recent onset. The diagnosis of pulmonary granulomatosis was made on the basis of lung biopsy which also demonstrated many intracellular Al dust particles. This case shares some similarities with the Chen report above. Morgan and Dinman (in Gitelman 1989) stated that there was little likelihood that Al was the cause of the conditions in these two cases. They cited the absence of this disease in "numerous epidemiological surveys of exposure to both metallic aluminum and alumina" as evidence weighing heavily against causality for Al.

Fernandez reported a 48 year old aircraft worker who had been an installing electronic equipment for 20 years. He developed PG with foreign bodies diagnosed by light microscopy of lung biopsy tissue. Special microscopic examination to determine the presence of Al could not be done. The author speculates that this man's disease could have been caused by Al. He considered Chen's report in so doing.

5. PULMONARY FIBROSIS AND ALUMINA FIBERS

Gilks and Churg (1987) reported pulmonary fibrosis in a 50 year old aluminum smelter worker with 19 years in the smelter, six years experience pouring ingots and five years of potroom experience. The onset of his disease was slow and progressive over a 5 year period, resulting in death from pulmonary insufficiency. Post mortem confirmed the diagnosis of pulmonary fibrosis. The lung demonstrated the presence of non-crystalline Al (Al oxide) as well as crystalline Al fibers (alpha type) smaller than 2 μ m.

This is the only case in the literature which suggests that Al oxide may lead to fibrosis of the lung. The authors stated: "Although there is no proof that fibrous aluminum is fibrogenic, the presence of this form of mineral has never been documented before in human lungs, and the potential action of large numbers of fibers of this type is unknown" (Gilks and Churg, 1987). There is little exposure to Al or to Al fibers (if they exist), in potrooms (Theriault, 1989). Gilks and Churg also mention that the total pulmonary dust load was high in this worker.

Pigott et al. (1981) exposed rats to two types of alumina fiber: refractory alumina and thermally aged alumina. Thermal ageing produces intracrystalline changes in the alumina. They were able to demonstrate that alumina fiber was minimally fibrogenic. They noted, however, that the reactions were more related to the fibrous structure than to the Al content (Pigott et al., 1981).

6. PULMONARY FIBROSIS AND ABRASIVES IN ONTARIO (SHAVER'S DISEASE)

Aluminum oxide (alpha aluminum oxide, alumina or corundum) is used in the manufacture of abrasives. Natural emery is composed of alumina and silica.

Chest x-ray abnormalities in workers making emery have been noted (Bech et al., 1965). This work was preceded by several reports of x-ray changes in abrasives workers (Clark, 1929; Smith and Perina, 1948; in Gitelman, 1989). However, exposure to free silica in all of the workers reported, as well as exposure to other metal dusts, confounded the relationship ascribed to Al in this occupation. By the time Shaver and Riddell reported their findings in 1947, the causal role of silica in the changes observed was believed to be stronger in this occupation (see below).

Shaver and Riddell (1947) reported pulmonary fibrosis in 35 of 244 workers engaged in the making of abrasives in four different plants in Ontario. Ten of the workers died of respiratory failure (Shaver and Riddell, 1947). The disease is characterized by (non-nodular interstitial) fibrosis which is rapidly progressive. Emphysema develops and there is a propensity to spontaneous rupture of the lung (pneumothorax). Shaver and Riddell stated: "The etiology is doubtful. It is known that the process involves exposure to high concentrations of alumina and silica, both in a very fine state of division, and to small quantities of many other substances" (Shaver and Riddell, 1947).

Shaver's disease is now considered to result not from Al but from exposure to free silica and in particular to cristobalite which is more fibrogenic than quartz (Morgan and Dinman, 1988).

4.2.2 EPIDEMIOLOGY OF LUNG DISEASE IN ALUMINUM MINING, PROCESSING AND HANDLING

1. GENERAL

There are several epidemiologic studies of the Al mining and refining work force. None of these studies refers directly to Al exposure but rather to the general work environment. No study concludes that the reported diseases are associated specifically with Al metal or any of its compounds. However, what follows needs consideration in the interpretation of such studies.

Dinman reviewed the experimental animal literature on alumina-related disease (Dinman, 1988). He concluded that "...low temperature transitional forms of alumina produce irreversible fibro-nodular change only when administered by intratracheal insufflation. Other aluminas not catalytically active, but also broadly defined as 'gamma' for different reasons also appear capable of inducing pulmonary fibrosis in the same model". Al_2O_3 , on the other hand, did not demonstrate a strong potential for generating fibrosis.

Aluminum oxide (alpha aluminum oxide, alpha alumina or corundum) is used in the manufacture of abrasives. Natural emery is composed of alumina and silica. Alpha aluminum oxide can be produced from the thermal dehydration of boehmite, an aluminum ore, at 1200°C . When treated with a temperature of 850°C , a highly reactive

transitional form of alumina is formed, designated by one researcher as gamma and described by others as more likely to be eta alumina (Dinman, 1988). Gamma to eta aluminas are a range of aluminas with various degrees of biological reactivity.

From the whole animal insufflation model where exposure can be well controlled and the substance identified as to molecular and crystalline structure as well as particle size, the following conclusions were derived by Dinman:

- exposure to catalytically active eta transitional alumina results in severe fibronodular alteration;

- exposure to catalytically inactive aluminas (alpha Al_2O_3 and gelatinous boehmite) produces a lesser but broader range of fibronodular change;

- it is inconsistent to associate gamma alumina with pulmonary hazard in view of the broad range of reactivity to various described gamma aluminas (i.e. zero response with gamma extending to severe alterations with eta transitional forms) and the minimal but consistent response to a fine alpha alumina;

- the work of Klosterkotter with extremely high doses of well identified gamma alumina was carried out at very high doses producing pulmonary alveolar proteinosis (PAP), a response which is non-specific and can relate to very high pulmonary loading to dusts of various types.

A pulmonary response, then, can be said to occur consistently only with catalytically active, low temperature range, transitional alumina and/or relatively high surface area (viz. very fine dust) alumina (Dinman, 1988).

Occupational exposure to aluminas is usually a mixed dust exposure, with silica for example in the case of Shaver's disease, and other dusts as discussed in some of the case reports. The species of alumina is rarely identified in occupational studies. An exception to this is the work of Townsend et al. (1988) described elsewhere in this review. Animal inhalation experiments using different alumina preparations demonstrated varied lung responses (Dinman, 1988). These are summarized in Table I. These results demonstrate that speciation of alumina is of utmost importance in the interpretation of results of epidemiologic studies since only some species of alumina have been demonstrated to be fibrogenic, and those only in the intact animal tracheal insufflation model. The occurrence of pulmonary alveolar proteinosis has been noted to be a non-specific response to high pulmonary dust loadings. The case reports described above would tend to support this interpretation as well.

2. SMELTER WORKERS

Chan-Yeung et al. (1983) carried out an epidemiologic survey of workers in an aluminum smelter in British Columbia, Canada. This consisted of a cross sectional survey of current workers (93.8% of

the work force, 6.2% refusal rate) using a questionnaire, clinical examination with spirometry and chest x-ray, and environmental monitoring. There were 713 in office and casting with no Al exposure; 302 potroom workers with medium exposure; and 495 potroom workers with high exposure.

After adjustment for age, height and smoking habit, high-exposure workers had a greater prevalence of cough and wheeze, lower mean FEV_1 and MMEFR than the lowest exposure group. (FEV_1 is the forced expiratory volume in the first second; MMEFR or maximal mid-expiratory flow rate now called the forced expiratory flow or FEF_{25-75} , also a measure of outflow obstruction). Medium exposure workers had a slightly greater prevalence of respiratory symptoms and lower lung function than the lower exposure group but the differences were not significant. Particulate air levels were below the standard but benzo-alpha pyrene levels were 3.49 ug/M^3 . Many workers had been miners, 60% had chest radiographs, 10 % had radiographic evidence of healed pulmonary tuberculosis.

The authors concluded that workers who spent 50% or more of their working time in potrooms had a significantly increased frequency of cough and wheeze and a significantly lower FEV_1 and MMEFR when compared to a control group adjusted for age and smoking status. Even though the ambient level of each of the many respiratory irritants found in the potrooms was within standards or guidelines, the authors suggested that the presence of many contaminants in the

work environment may explain the differences found (Chan-Yeung et al., 1983).

Martin et al. reported a prevalence (or cross-sectional) study of respiratory disease in workers in the primary Al industry (tank rooms or potrooms of the Soderberg refining process) in Quebec. Preliminary results demonstrate that the prevalence of bronchial obstruction is higher in the potroom exposed workers as compared to controls regardless of smoking status. Smoking was demonstrated to have an additive effect on the risk of respiratory disorders (Martin et al., 1988).

Townsend et al. (1988) carried out a cross-sectional survey examining the chest x-ray abnormalities, smoking and dust exposure among workers in the mining and refining of alumina in a United States company. The aluminas of interest were low temperature range transitional aluminas, but the authors admit that exposure to a wide range of aluminas is inevitable under the conditions of production in this study population (Townsend et al., 1988). Only non-smokers and current smokers were reported. Among non-smokers with low dust exposure, there was no trend in the prevalence of lung opacities with age and increasing duration of exposure. Non-smokers with higher dust exposures showed a trend to increasing opacities with increased duration of exposure. The rates for smokers were higher in each category of exposure and duration of exposure. Seven to 8% of aluminum workers in this cohort had x-ray

findings of scanty, irregular lung opacities the prevalence of which was higher among smokers as compared to non-smokers. It was also higher in non-smokers with higher cumulative dust exposures.

Gibbs reported the mortality experience of Al reduction plant workers (two cohorts, one of 5,406 men from 1950 and the other of 485 men in a second plant from 1951 both followed to December 1977). No death in the first cohort was due to pneumoconiosis. However, when compared to Quebec males, there was an excess mortality of respiratory disease, pneumonia and bronchitis (Gibbs, 1985).

Rockette and Arena (1983) reported the mortality experience of 21,929 workers with five or more years experience in Al reduction plants. Mortality from non-malignant respiratory disease was not elevated (overall SMR 91, influenza and pneumonia excluded SMR 102.1). There was no significant excess of bronchitis. However, men with 20 or more years experience in the prebake process demonstrated an elevated rate of asthma (SMR 260.2) while Soderberg working men had an excess mortality from emphysema (potroom workers SMR 194 and carbon plant workers SMR 267.1). The pattern of emphysema mortality was not as clear in prebake method workers as in Soderberg method workers but the authors consider the data suggestive of a similar mortality pattern.

Edling et al. followed for 25 years the mortality and cancer incidence of a cohort of workers in an abrasive (Al_2O_3 and carborundum- SiC) manufacturing industry. They did not find any significant incidence of non-malignant respiratory disease (Edling et al., 1987).

Milham reported mortality in a cohort of aluminum reduction workers in six plants in northwest United States (Milham, 1979). He found a low all cause mortality (SMR 86), but an elevation in several specific categories: lung cancer (SMR 117), pancreatic cancer (SMR 180), lymphatic and hemopoietic cancers (SMR 284), fatal benign tumors of the brain (SMR 391) and pulmonary emphysema (SMR 204). Job-relatedness was suggested for lymphatic cancers and emphysema through further analysis for latency, length of employment and job category.

4.2.3 SUMMARY: HEALTH EFFECTS OF AL ON THE LUNG

A number of pulmonary conditions can result from exposure to aluminum-related workplace environments: industrial bronchitis and asthma and abnormalities of pulmonary function which are likely the non-specific effect of inhalation of inert dust particles or of fumes.

Pulmonary alveolar proteinosis (PAP), desquamative interstitial pneumonitis (DIP), and pulmonary granulomatosis (PG) are non-specific pathologic reactions to a variety of dusts. The relevance of the presence of Al in pathologic

specimens of a small number of unrelated cases in the literature is uncertain.

Pulmonary fibrosis following alveolitis (inflammation of the air sacs) results from exposure to powdered aluminum only in workers exposed to fine pyro powders coated with mineral oil.

Pulmonary fibrosis occurs also in the manufacture of abrasives (Shaver's disease). This is currently thought to result from exposure to cristobalite silica, not to alumina.

There are alumina species which can cause pulmonary fibrosis in the intratracheal insufflation animal model. These are in particular, catalytically active, low temperature transitional forms of alumina. These species may occur in the smelting and processing of aluminum but not in its secondary uses. The effects demonstrated in animals have never been demonstrated in humans. Under the usual conditions, "occupational exposure to a broad range of aluminas indicates - at most - minimal pulmonary nodular response" (Dinman, 1988).

The mortality experience of Al reduction workers demonstrates an excess of respiratory disease, pneumonia and bronchitis (Gibbs, 1985); elevated rate of asthma in 20+ year workers (Rockette and Arena, 1983); excess mortality from emphysema in potroom and carbon room workers (Rockette and Arena, 1983); non-malignant respiratory disease (Edling et al., 1987; Gibbs, 1983), and pulmonary emphysema (Milham, 1979). Milham suggested work-relatedness for pulmonary emphysema and for lymphatic and hemopoietic cancers.

4.3 THE CENTRAL NERVOUS SYSTEM AND ALUMINUM

Concern about the neurological toxicity of Al in the occupational setting first arose in the late 1950s. The case which initiated that concern is discussed below. Subsequent case reports not related to occupational exposure follow.

4.3.1 CASE REPORTS

The first case of encephalopathy attributed to Al was reported by McLaughlin in 1962 and is discussed above as the index case of a cluster of pulmonary fibrosis in the pyrotechnics industry (Mitchell et al., 1961). It is noteworthy that even though there are insightful reports which support the association of fibrosis to Al powder (coated with mineral oil), no case of neurological disease or syndrome was uncovered in any of the exposed workers by any of the investigators even though this was specifically looked for (McLaughlin et al., 1962). McLaughlin did not report the level of alcohol consumption of this patient. The brain did not demonstrate neurofibrillary tangles but did have elevated Al levels.

Lapresle et al. (1975) and Duckett et al. (1976) reported an unusual case of dementia in a severe alcoholic without past contact with Al. The 27 year old man presented with progressive mental deterioration leading to death 10 years later. Pathological examination of the brain and other organs revealed elevated levels of several metals: iron, phosphorus, sulphur, calcium and aluminum.

The authors remark that metals tend to accumulate in the tissues in certain degenerative diseases, but they had never observed such a marked accumulation of Al in all tissues. It is not clear what conclusions regarding Al and dementia can be drawn from this unique case.

Recently, a Toronto research group reported the case of a 42 year old man with atypical motor neuron disease who had exposed himself more than 20 years to a facial cream containing 38% Al oxide (Ross et al., 1986). Evidence for Al overload consisted of sustained urinary excretion of Al with chelation therapy and clinical improvement after treatment over a six month period (Ross et al., 1986; Kruck and Crapper McLachlan, 1989).

Only the above reports were found involving persons with normal kidneys and concurrent presence of significant amounts of aluminum in the body and clinical neurological disease. One case occurred in an occupational setting which no longer exists (the pyro powder industry); the second was of unknown cause but no occupational exposure to Al was known; and the third may have resulted from self-administered skin cream exposure. In the first two cases, increased body burden was documented at autopsy. In third case, the evidence for increased body burden is the results of chelation therapy.

Longstreth et al. reported his study of three aluminum smelter potroom workers who developed neurological disease (Longstreth et al., 1985). Two developed cognitive defects: all three had incoordination and intention tremor; the most severely affected had spastic paraparesis (paraplegia). The clinical features were quite different from those in dialysis dementia; bone aluminum levels are not reported. The cause of the disorder in these men has not been found though the relationship to some exposure in the potroom remains a possibility.

4.3.2 THE DEMENTIAS

1. GENERAL

Dementia is defined as the organic loss of intellectual (thinking) function. Cognition (from the Latin *cognoscere*, to know) is that operation of the mind by which we become aware of objects of thought and perception and includes all aspects of perceiving, thinking and remembering (Dorland's Medical Dictionary, 1985).

Different aspects of cognitive function may be impaired in different conditions:

- functional (non-organic) psychiatric conditions such as depression and schizophrenia:
- intoxication from drugs (alcohol, barbiturates, hallucinogens):
- hydrocarbon solvents:

endocrine disorders (hyper and hypothyroidism, pituitary insufficiency, hyperinsulinism, hyper and hypoparathyroidism); nutritional disorders (B_2 , thiamine, folate and niacin deficiency); organic loss of brain tissue from trauma or cerebrovascular insufficiency (hypertension, atherosclerosis and stroke); and specific pathologic states such as slow-growing brain tumour, normal pressure hydrocephalus, Parkinson's disease, Alzheimer's disease, or just "normal aging" (Plum, in Katzman 1978; Plum, 1979).

Alzheimer's disease (SDAT) is a brain disorder characterized clinically by a progressive dementia that occurs in middle or late life (McKhann et al., 1984). There occurs a progressive deterioration of memory from mild forgetfulness (forgetfulness stage) and disorientation (confusional stage) to frank dementia. The intellectual and motor deficits have broad range as the disease progresses and tests applicable to each phase which allow measurement of the progression of the disease vary considerably (Crapper McLachlan et al., 1984). The typical clinical picture is used in conjunction with laboratory studies to make the diagnosis of SDAT, largely a diagnosis of exclusion.

Alzheimer first described the pathological picture of SDAT in 1907: neurofibrillary degeneration of cortical and hippocampal neurons with large numbers of neurofibrillary tangles (NFT-- dense bundles

of fibers within the nerve cell) and senile (neuritic) plaques in the brain (DeBoni and Crapper McLachlan, 1980; Perl, 1985). The loss of neurons results in cortical atrophy and may produce dilated cerebral ventricles. More recently, the structure of NFTs and neuritic plaques has been examined. NFT and plaques contain 10 nm filaments in pairs (paired helical filaments--PHFs) of uncertain chemical composition. They react with antibodies to normal filaments and have immunological cross-reactivity to amyloid. Amyloid is found in cerebral, hippocampal and meningeal blood vessels. These PHFs also occur in Guam ALS-PD (but not in non-endemic ALS), post encephalitic parkinsonism, dementia pugilistica (boxer's dementia) and Down syndrome (Wisniewski and Iqbal, 1980). Neuritic plaques also occur in the infectious brain diseases scrapie, kuru and Jakob-Creutzfeldt. Anatomic areas with NFTs contain increased amounts of A1, primarily in the nucleus of degenerating neurons attached to nuclear chromatin, not in the cytoplasm (Crapper McLachlan et al., 1980). Some authors have questioned the finding of elevated A1 in the brain of SDAT cases because of the inconsistency of results encountered among laboratories (Perl, 1985). These differences have been attributed to a tissue sample size problem (Krishnan et al., 1988). The larger the amount of tissue required by the analysis, the more likely a lower result. If small samples of tangle-bearing tissue are analyzed, A1 is consistently elevated.

Intellectual impairment (cognitive deficit), regardless of the cause, can be measured by a variety of clinical test instruments. As more clinical instruments become available, it is possible to arrive at a reasonably accurate specific diagnosis for SDAT before death with the use of supplementary laboratory tests including the CAT (computerized assisted tomography) scan which demonstrates organic loss of brain tissue, and by psychometric exams without necessarily resorting to biopsy. Organic loss of brain tissue as diagnosed by CAT scan alone may not herald cognitive defects. The predictive value reported to date for clinical tests, CAT scan included, ranges from 55% to 82% (Rocca et al., 1986). The definitive evidence of the cause of an organic cognitive defect may be found in histopathological examination of the brain with the finding of pathognomonic changes described above.

Several hypotheses regarding the etiology of SDAT are of current interest. Evidence to date does not support one hypothesis over another as the major factor explaining the occurrence of the disease. The study of other diseases where Al does play a role is helpful in understanding its possible relationship to SDAT.

2. DIALYSIS ENCEPHALOPATHY SYNDROME (DES)

Al has been implicated as the cause of the dialysis encephalopathy syndrome (DES). This syndrome was first characterized by Alfrey et al. in 1972. It consists of the onset of speech difficulties and changes in the electroencephalogram followed in a few months by

the development of a frank metabolic encephalopathy. [Metabolic encephalopathies may occur in the presence of many metabolic disturbances such as liver failure. The clinical picture includes loss of coordination, a characteristic flapping tremor, involuntary shaking, contractions of groups of muscles, loss of memory and personality changes.] Death usually ensues within several months.

This disease has been reported from dialysis centers throughout the world as small epidemics (Wisniewski and Sturman in Gitelman, 1989). It occurs in geographic areas of high Al concentration in tap water before it became common practice in dialysis centers to treat tap water by deionization or reverse osmosis to remove all trace elements before use in dialysis fluid.

Al content in the body and in the brain of renal failure patients who develop dementia is consistently high, higher than in dialysis patients who do not develop the disease. These patients also have elevated total body aluminum. Although DES patients have elevated levels of Al in the brain, it does not demonstrate any particular cellular pathology (Wisniewski and Sturman, 1988). The brain Al concentrates in small structures (lysosomes) in the cytoplasm (the fluid between the nucleus of the cell and the cell membrane) of the nerve cells (Crapper et al., 1980).

DES may occur in renal failure patients who are not undergoing regular dialysis and may be spare some dialysis patients receiving

treatment with the same water as those who develop the dementia. Al-containing antacids used to bind phosphate in the gastrointestinal tract of renal failure patients may be the source of Al in the CNS of patients with dementia. However, dementia does not occur in all patients receiving high doses of Al antacids regardless of treatment with dialysis (Wisniewski and Sturman, 1988).

Reduction of body Al through various treatments in patients with DES has had mixed results from no change to marked regression of the disease (Wisniewski and Sturman, 1989). The removal of Al from water used for dialysis resulted in the disappearance of the outbreaks of DES so that its epidemiologic relationship, if not its actual mechanism of action, is established and is not much disputed. The factors in each individual which provide a variety of outcomes with similar exposure are not well understood. This sustains much current research effort.

3. AMYOTROPHIC LATERAL SCLEROSIS (ALS OR LOU GEHRIG'S DISEASE) AND PARKINSONISM WITH DEMENTIA (PD)

These diseases are of interest in the study of SDAT because they share certain brain changes. Neurofibrillary tangles, amyloid, and elevated Al occur in both. Senile plaques containing a double helical structure referred to as an amyloid core or as paired helical filaments (PHFs) occur only in SDAT but not in ALS or PD.

The histopathological picture is also similar, but not identical. Al and calcium accumulate in the cytoplasm and nucleus of the cells in the neurofibrillary tangles of ALS-PD (Yase, 1974; Perl, 1985; Duncan et al., 1988) while Al accumulates in the nucleus of cells in SDAT. The presence of senile plaques and amyloid are also a characteristic of two other neurological degenerative diseases which will not be discussed here, Jacob-Creutzfeld and kuru, caused by infectious agents. The leading hypotheses regarding the cause of the ALS-PD complex are toxicity from a chemical in food and an interaction of metals in food and environment with other environmental or genetic conditions.

Areas of high incidence of amyotrophic lateral sclerosis (ALS) and parkinsonism with dementia (PD) occur in the Chamorro indians of the islands of Guam and Rota, in the Japanese of the Hobara and Kozagara districts of the Kii peninsula of Japan and in the Auyu and Jaqai (or Jakai) people of western New Guinea. Soil and drinking water in these endemic areas of ALS and PD contain above normal levels of Al and low calcium and magnesium. Calcium deficiency is reported to be prevalent in the same areas. These environmental conditions gave rise to one of the leading hypotheses on the etiology of ALS-PD, metal toxicity or an interaction of metal toxicity with other environmental conditions.

Another leading hypothesis of etiology in ALS-PD arose out of the knowledge that seeds of the false sago palm, *Cycas circinalis*, are

used as food or medicine in ALS-PD endemic areas: as food and medicine in Guam and as medicine in other endemic areas. These seeds contain a neurotoxic amino acid (beta-N-methylamino-L-alanine-- BMAA) which induces a disease in (cynomolgus) monkeys with features similar to ALS (Spencer et al., 1986). These experiments were repeated, but results differed (Dastur et al., 1974).

Lathyrism (paraparesis), a syndrome similar to ALS-PD, occurs in areas of Asia and Indonesia where the chickling pea (*Lathyrus sativa*) is used as food, usually in times of drought. This pea contains a neurotoxic amino acid (beta-N-oxalylamino-L-alanine-- BOAA) related to the cycad BMAA capable of reproducing the human disease in monkeys as well (Spencer, 1987a). Lathyrism has a short latency period after the consumption of the chickling pea starts and a self-limiting course once consumption of the pea stops.

Currently, the cycad hypothesis has been challenged, leaving the metal hypothesis dominant (Garruto et al., 1988a; Garruto et al., 1985). Garruto et al. carried out cycad and low Ca-feeding experiments on monkeys. They were able to induce neurofibrillary tangles (among other lesions) in the brains of monkeys fed low Ca-high Al and manganese diet without cycads. This investigator holds that endemic ALS-PD results from a "...basic defect in mineral metabolism which ultimately impairs axonal transport of

neurofilament proteins, leading to NFT formation" (Garruto et al., 1988b).

Gresham et al. carried out a case-control study of 66 San Diego area patients with ALS (Gresham et al., 1986). The investigators searched for potential exposure to heavy metals, including Al. They found no association between heavy metal exposure and ALS.

In support of the plant toxin hypothesis, individuals from the endemic areas may develop the disease long after their departure (Spencer et al., 1986; Deary and Whalley, 1988), suggesting a latency period between exposure and disease, and by inference, a slow acting neurotoxin. The decreasing incidence of ALS-PD in endemic areas is hypothesized to be related to changes in dietary practices and medicinal uses of the suspect seed (Spencer 1987b; Deary and Whalley, 1988).

In contrast to the evidence for causality for an environmental plant toxin in these motor neuron diseases, the evidence linking Al is primarily ecological: Al may be in the environment (food water) and the disease occurs in the same environment, but the actual exposure of each individual is unknown. The presence of elevated Al levels in the brain of individuals with degenerative brain disorders remains to be differentiated as a primary phenomenon (i.e. causal factor) or secondary phenomenon (resulting from the disease) (Crapper McLachlan et al., 1986).

4. ALZHEIMER'S DISEASE (SDAT)

HYPOTHESES REGARDING THE CAUSE OF SDAT

HEREDITY

There is a hereditary component in the etiology of SDAT. The pattern of inheritance appears to be autosomal dominant, but is likely more complex. The genetic hypothesis is supported by the following studies:

- at least 33 pedigrees (reports of families with more than one person affected);
- follow-up studies in twins and siblings;
- population-based studies (in Rocca and Amaducci, 1988);
- case-control studies (Heston et al., 1981; Whalley et al., 1982; Heyman et al. 1984; Amaducci et al., 1986; Shalat et al., 1987);
- abnormalities found in chromosome 21 in the relatives of SDAT cases, and of (Heston, 1976) chromosome 6 and 14 (Weitkamp et al., 1983);
- cases of early onset SDAT occur in families:
- Down syndrome (Heston, 1976, Heston et al., 1977; Heston et al., 1981): probably all Down syndrome patients eventually develop Alzheimer lesions in the brain if they live beyond age forty: the locus conferring susceptibility in familial Alzheimer's and the amyloid gene locus both occur in chromosome 21 and Down syndrome is a duplication of chromosome 21.

The literature consistently demonstrates heredity and head trauma as major risk factors for SDAT (Heyman et al., 1984; French et al., 1985; Mortimer et al., 1985). Dementia pugilistica (boxer's dementia) demonstrates neurofibrillary tangles with the double helical structures known as PHFs. This lends support to the idea that tangles result from many types of cell injury. Current work has focussed on mechanisms, some of which may be inherited, which allow the cell to accumulate metabolic products or xenobiotics such as Al and other metals, which may have a deleterious effect on the cell.

. IMMUNE MECHANISMS

Torack and Gebel (1983) present evidence in support of an immunological hypothesis. This evidence is indirect in that it is sought in conditions that are distantly related to SDAT, namely amyloidosis (Torack and Gebel, 1983). The rationale for this is the presence of amyloid fibers in many tissues in patients with idiopathic amyloidosis and in the neurofibrillary tangle and senile plaque of SDAT.

Senile plaques are composed largely of amyloid, a complex glycoprotein whose protein component is made up of immune globulins or their fragments. The tau fragment of immunoglobulins has been identified in the filaments within the tangles and plaques by immunologic techniques (Brion et al., 1986). Conditions which affect the immune system produce amyloid. The association of SDAT

with immunological conditions has been examined epidemiologically in case-control studies. Heston et al. reported an association of SDAT with a family history of lymphoma, lymphosarcoma, Hodgkin's disease, and other immune system disorders (Heston et al., 1981).

TRANSMISSIBLE INFECTIVE AGENT

Scrapie, a neurological disease of sheep, kuru and Jakob-Creutzfeldt disease are caused by infectious agents (slow viruses). The organism for scrapie has been identified but not for kuru and JCD. JCD and SDAT have some clinical, pathological and epidemiologic similarities. Of pathological importance is the consistent occurrence of NFTs and neuritic plaques in SDAT but not in JCD.

Brown (1987) discusses the three possible organisms which may be related to slowly-progressive degenerative brain disorders: the prion, the virino (a low molecular weight nucleic acid with protein derived from the host), and the scrapie nucleic acid (Brown 1987).

METAL TOXICITY (ALUMINUM)

Al plays an important role in ALS-PD, DES and SDAT although the evidence for causality is strong only for DES. Evidence supporting metal toxicity comes from experimental data on animals (NFTs form with Al injection into the brain or with incubation of brain cells in vitro); Al has many detrimental effects on the metabolism of the nerve cell; clinical and experimental studies in DES strongly

support Al toxicity as the cause: Al gains access to brain cells in SDAT and ALS-PD: a positive ecological correlation has been found between dementia as a cause of death or morbidity and environmental (water) levels of Al. However, there is still a major gap in our understanding of how Al gains access into the cell. Much current work focusses on this.

EPIDEMIOLOGY OF NON-DIALYSIS DEMENTIA

It is difficult to estimate the prevalence of dementia partly because there is no agreed upon case definition (the level of impairment at which a person is labeled as having the disease with reasonable certainty). Demographic changes influence prevalence and studies have not been robust enough to provide firm answers (Ineichen, 1987; Rocca et al., 1986). It is a disease of aging with no gender preference. In contrast to all dementias, it appears that SDAT has a preference for females. Death certificate (mortality) data are not reliable because dementia may not be recognized as a contributory cause of death (Rocca et al., 1986). Analytic studies (primarily case-control in this disease) suffer in that the diagnosis is presumptive (see sensitivity and specificity of diagnostic tests below) and the informant is the spouse or relative, not the sufferer. Bias may occur in that members of the same family may go to the same hospital (selection bias), family of cases may have a heightened awareness of other cases (awareness bias), and family aggregation may result from similar environmental conditions (Rocca et al., 1986).

If it is difficult to measure the prevalence of dementia in general, then Alzheimer's disease, a specific type of dementia, may be as elusive. The sensitivity (the ability to detect persons with the disease) of available diagnostic procedures is about 70% and the specificity (the ability to detect persons without the disease) from 72% to 78%. Rocca calculates the predictive value of a positive clinical diagnosis is then between 55% and 82% (Rocca et al., 1986). This figures in the design of studies because the predictive value depends on prevalence rate. The studies which attempt to link prevalence of dementia to environmental conditions are limited because there is always the possibility that cases of dementia may be erroneously assigned to different diagnostic categories. Many clinical diagnostic instruments are used to enable the examiner to make a diagnosis with a high degree of accuracy in individual cases. However, brain biopsy showing the specifically distinctive (pathognomonic) changes of senile plaques and neurofibrillary tangles in specific areas of the brain is still the "gold standard" for diagnosis of SDAT. Tissue is not always available, however.

ECOLOGICAL STUDIES

Ecological studies use variables applicable to a group of individuals (viz. water Al concentration in drinking water), and not to individuals themselves (viz. individual exposures). These studies have been pursued in different countries. The biological

relevance of the Al hypothesis in ecological studies rests on the following findings:

- Al is consistently elevated in the brain of SDAT victims (but not in the brain of other dementias) and SDAT consists of about 70% of all dementias. Specifically Al is present in the neurofibrillary tangle and senile plaque (the diagnostic lesions of Alzheimer's disease).

- Al is mobilized into water and vegetation from the environment under certain conditions (acid rain leads to the precipitation and leaching of Al from rocks into ground water). Al levels in drinking water depend, therefore, on the naturally occurring content, the content from acid rain leaching and the contribution from the use of Al salts as coagulants in water treatment.

- Al is a neurotoxin when injected directly into the brain of experimental animals.

The existence of good mortality statistics and population-based registries theoretically allow the correlation of outcome (mortality by cause) to an exposure variable of interest (water source or water Al level, etc.)

The Norwegian Ministry of the Environment carried out an ecological study using readily available data bases (cancer registry, death statistics, and water quality statistics) to study the relationship of water Al (in acid precipitation impact areas) and the occurrence of dementia (Vogt, 1986).

Vogt (1986) found that there was a relationship between the concentration of Al in drinking water and mortality rates from "Alzheimer's/Alzheimerlike diseases" (defined as death from the causes: senile dementia or presenile dementia). Average annual mortality rates for "age-related dementia" were calculated from vital statistics and other information (including survey data from psychiatric nursing homes). Age-related dementia was defined as senile dementia (including primary cause deaths among people 70-years of age with various early and late stage symptoms of dementia) and presenile dementia (including deaths among those under 65). However, the specific methods used to compile the mortality statistics were not presented. Mortality rates for age-related dementia as the primary cause of death increased significantly with Al concentration in the water. Vogt is careful to add that this "... co-variance must not be regarded as proof of an existing linkage between Al in drinking water and Alzheimer's/Alzheimerlike diseases. However, the study suggests that further scientific studies should be undertaken - and indicates a potential area of concern..."

More information on methods is available in a new study by Martyn et al. (1989) from England which is quite similar to the Vogt study in Norway above. Here, Alzheimer's cases were accessed from information on CAT scan request forms provided to diagnostic laboratories.

Martyn's source for cases of dementia was the centers carrying out computerized tomography (radiological brain scans). Additional information was sought on each diagnosed case in order to be able to assign it to the following groups: probable Alzheimer's disease, possible Alzheimer's disease, cerebrovascular dementia, dementia of other causes. The definitions used vary from those now used in epidemiologic studies. Verification of the method of assigning cases to the probable Alzheimer's disease category was established in 19 of 24 cases based on the final clinical diagnosis in 52 consecutive cases in one center. Using age- and sex-specific population data for England and Wales in 1983, the incidence of SDAT was standardized for each county district in the study. Water Al was estimated from data from the previous 10 years maintained by the local water authority of 88 counties in England and Wales. A statistical model linking risk of SDAT with Al water content was estimated.

There was excess risk among patients aged 40-69 from all causes of dementia in all groups of districts where Al water concentrations were above 0.01 mg/L. The increased risk was confined to one diagnostic category, probable Alzheimer's dementia. If patients over 65 were excluded, the relative risk in the highest water Al group (>0.11 mg/L as compared to the lowest (0.01 mg/L) was 1.7 (95% confidence interval: 1.1 - 2.7), but there was no risk gradient between concentrations of Al from 0.02 to 0.11 mg/L.

The authors conclude: "The results of the present survey provide evidence of a causal relation between aluminium and Alzheimer's disease. However, care is needed in the interpretation because, as in all epidemiological surveys, the possibility exists that the relation observed is due to the operation of some unknown confounding variable. Further studies in different populations are required to confirm these results and we are now conducting a case-control study to investigate the relation between dietary aluminium and Alzheimer's disease at an individual level" (Martyn et al., 1989).

The authors' conclusions are inappropriately strong considering the study design and the lack of dose-response relationship. Alzheimer's disease can only conclusively be diagnosed at autopsy; and clinical confirmation usually requires demonstration of deterioration in at least two consecutive examinations separated in time by at least six months. Moreover, ecological studies can result in erroneous conclusions when group data are used to make statements of causality about individuals (this is the ecological fallacy; see Piantadosi et al., 1988). This fact is indirectly acknowledged by the authors in their description of the type of study which they intend to carry out next (a case-control study). Several case-control studies have been carried out in a search for specific risk factors for SDAT discussed in the section which follows.

CASE-CONTROL STUDIES

Rocca et al. reviewed the epidemiologic literature up to 1985 and summarized the risk factors found in eight case-control studies (Rocca, 1986). Four demonstrated a consistent association with a family history of SDAT and with Down syndrome (Heston, 1981; Whalley, 1982; Heyman, 1984; Amaducci, 1986). Of these, one also demonstrated a significant association with head injury (Heyman, 1984). The studies which follow were not included in Rocca's review and are presented separately.

French et al. (1985) carried out a case-control study of SDAT. Seventy-eight cases were drawn from the Veteran's Administration Medical Center in Minneapolis. Diagnosis was by a single examiner using both inclusion and exclusion criteria for each case diagnosed. Patients with a psychiatric or alcohol abuse history were excluded. Controls were drawn from the hospital and the patient's neighborhood, matched for age, sex and race. Interviews of patient surrogates, usually a spouse, were carried out. Interview information gathered encompassed variables relevant to viral, genetic, occupational and environmental exposures, drug use, psychologic stress, smoking, and alcohol consumption. After exclusion of chosen controls for various reasons, 76 pairs (cases and hospital controls) and 46 pairs (cases and neighbourhood controls) were available for analysis. The major finding in this study was the greater occurrence of head trauma among cases. There were no statistically significant differences in occupational

exposures of cases and hospital or neighborhood controls. The finding of head trauma as a possibly important risk factor was also found in a study by Heyman et al. (1984) discussed above.

Shalat et al. (1987) also carried out a case-control study to look at risk factors for Alzheimer's disease. Risk factors considered were family history, thyroid disease, head trauma, and others. Cases were obtained from the Geriatric Research, Education and Clinical Center at the Edith N. Rogers Memorial Veterans Hospital in Bedford, Massachusetts. The diagnosis was based on criteria set forth in the DSM III (Diagnostic and Statistical Manual of Mental Disorders, 1980) and on ADRDA (Alzheimer's Disease and Related Associations, McKhann et al. 1984). Neighbourhood controls were selected. The spouse or the person living with the study participant was the informant. The data collection instrument was a self-administered questionnaire.

One hundred and six cases (77%) and 214 (33% of eligible) controls were considered in the analysis. Some controls were excluded because of heavy alcohol use (>20 drinks per week) and some cases were excluded because autopsy confirmed a different diagnosis. A matched analysis was carried out on 98 cases and 162 controls.

A significant excess of family history of SDAT or other dementia was found among the cases. Clinically observed depression was also more common among cases than controls. Smoking was reported more

frequent among cases than controls and was a significant risk factor at the 1 - 2 pack per day level. Cases were more likely than controls to be at least 1 pack per day smokers. There was an increased trend in the risk with increasing cigarette consumption. However, when cigarette smoking status was dichotomized (yes or no), no statistical difference was found among cases and controls. Methodological difficulties regarding control response rates are discussed. No reference is made in this publication to occupational risk factors, water source or water Al level.

Shalat examined occupational risk factors in the same group of patients in a subsequent publication (Shalat et al., 1988) using the voter registration list for age-, sex-, and residence-matched controls, and open-ended and directed questionnaires seeking occupational history and exposures. The study focussed on lead and solvent exposure, not on aluminum. No association was found between Alzheimer's disease and ever having occupational exposure to organic solvents or lead.

English (1985) and Corkin (1983) examined the hypothesis that maternal or paternal age may be related to the development of SDAT. They found no support for this hypothesis in their case-control studies. However, Cohen (1982) reported a case-control study of a group of Alzheimer's patients born between 1891 and 1921: the median age of the mother was 35.5 years, and of the father, 38.0 years. Randomly selected persons from the 1907 birth registry had

the mother's median age of 27.0 years, a significant difference (Cohen, 1982).

Borenstein Graves examined risk factors in 130 Washington State residents with pathologically confirmed SDAT. This case-control study examined family history of SDAT, head trauma, viral and immune agents, other factors, and Al consumption (analgesics, antacids and antiperspirants). The relative risk estimates of Al-containing antiperspirant use were 3.1 ("low" use), 3.1 ("medium" use), 3.2 ("high" use). The author points out, however, that only 48% of respondents had information on antiperspirants, and the validity of the response was low (Kappa statistic = 0.22). Elevated odds were found for use of all antacids, but this elevation was not sustained with Al-containing antacids alone. The validity of the response was higher than for antiperspirants, however (Kappa statistic = 0.63) (Borenstein Graves, Ph.D thesis, 1989).

The interpretation of case-control studies is fraught with uncertainties, in large part because of the difficulty in establishing reliable exposure histories among both cases and controls. This difficulty is particularly heightened for SDAT cases since surrogates (viz. family members) provide the required information for the case. Case-control studies can provide valid support for previously stated hypotheses. Some of the studies described above do this but others must be viewed as hypothesis-

seeking exercises. No new hypotheses have emerged from case-control studies published to date.

MORTALITY STUDIES

Gibbs reported the mortality experience of two Canadian cohorts of aluminum smelter workers and found no deaths from Alzheimer's disease (Gibbs, 1985).

A re-analysis of Rockette and Arena's cohort of Al reduction workers examined mortality from neurological causes of death (Memorandum to B. Dinman from Rockette, February 14, 1986). The number of deaths due to seven neurological causes was small (14). This analysis does not provide evidence for or against an occupational relationship between aluminum smelting and death from a neurological, possibly dementing illness.

APPENDIX 1

ANALYTIC METHODS

Analytic techniques for Al include atomic absorption (AA) (2 methods), atomic emission spectroscopy (AES) (6 methods), spectrophotometry (3 using fluorescence, 1 with electron device), neutron activation analysis, gas chromatography (GC), electrochemical methods, mass spectrometry and a variety of coupled methods intended to increase sensitivity and/or decrease background noise (Skalsky and Carchman, 1983; Jaworski, 1986). The results obtained are method-dependent and the precision (i.e. the ability of a method to reproduce a result) varies from 2.5% to 13%. Atomic absorption spectroscopy tended to produce values in the lower range while neutron activation analysis resulted in higher values. The authors advise a careful interpretation of all results, especially taking into consideration the method used and the assignment of normal or abnormal to a particular value. Meticulous care must be taken with blank controls as Al contamination of samples may occur relatively easily during sampling, storage and analysis.

Although many methods are useful in the analysis of geological and metallurgical samples, Jaworski stresses that only three methods are acceptable for Al analysis in biological samples: atomic absorption, atomic emission spectrometry, and gas chromatography with electron capture (Jaworski, 1986). Interlaboratory comparisons of analyses of Al in distilled water and natural water varied from 19% to 147%. All laboratory results should therefore

be scrutinized meticulously before clinical interpretations are provided.

TABLE 1
Review of Experimental Data with Contemporary Evaluation of Alumina Species

Investigator	Agent Investigator Designation	Identity (1987)	Crystalline Packing Arrangement	Route of Administration	Particle Size, μ m	Surface Area m ² /g	Catalytic Activity	Dose, mg	Response
Gardner et al.	C-730, activated HX1010	X transitional Gelatinous boehmite	γ γ^*	Inhalation Inhalation	? 0.02	250-? 250-350	- -	21-23 m ³ 35-105 m ³	No harmful effects No harmful effects
King et al.	γ -ALOOH HX1010	Gelatinous boehmite	γ^*	Intratracheal insufflation	0.02-0.04	250-350	-	100	+3 to +5% fibrosis [†]
Stacy et al.	γ -ALOOH HX1010	Gelatinous boehmite	γ^*	Intratracheal insufflation	0.02-0.04	250-350	-	50	+3 fibrosis [†]
	γ -Al ₂ O ₃ at 850°C	η transitional	γ	Intratracheal insufflation	0.02-0.04	60-?	-	50	5-5 fibrosis [†]
	γ -ALOOH Cerahydrate ^o	Boehmite	γ	Intratracheal	3	0.6	-	50	0 fibrosis [†]
	α -Al ₂ O ₃ HX1010 at 1,200°C	α -Al ₂ O ₃ (corundum)	α	Intratracheal insufflation	0.1-0.8 [*]	3	-	50	-1 fibrosis [†]
Flosterkötter	γ -Al ₂ O ₃	γ transitional	γ	Intratracheal	0.005-0.04	95-105	-	35	+3.5%
	γ -Al ₂ O ₃	γ transitional	γ	insufflation Inhalation	0.005-0.04	95-105	-	3300/m ³	Alveolar proteinosis [‡]

^o This alumina is only minimally crystalline.

[†] System of fibrosis grading of King et al.

^{*} Estimated by review of electron micrographs of Stacy et al.

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HEALTH EFFECTS OF ALUMINUM IN THE WORKPLACE:

REVIEWERS' COMMENTS

Industrial Disease Standards Panel
October 18, 1989

HEALTH EFFECTS ON ALUMINUM IN THE WORKPLACE:

REVIEWERS' COMMENTS

FOREWORD

This document contains the verbatim comments which were solicited by the Panel from:

Dr. N.M. Cherry	Neurobehavioral Research Unit, McGill University;
Dr. W.K.C. Morgan	University Hospital, University of Western Ontario;
Dr. P.S. Spencer	Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University; and
Dr. G. Thériault	School of Occupational Health, McGill University.

These comments addressed the content of Dr. L.F. Smith's initial draft of 'Health Effects of Aluminum in the Workplace'. The final version of Dr. Smith's paper has incorporated these comments as follows:

1. Morgan and Thériault commented on the fact that the aluminum (Al) prophylaxis provided to Northern Ontario miners consisted of atomized particles of oxidized Al metal (i.e. Al oxide) and not aluminum hydroxide dust. This was corrected throughout.
2. Thériault recommended separating the health effects found in primary aluminum production (smelting industry) from those found in mining and in secondary manufacturing. He also recommended mentioning bladder cancer, skin telangiectases and fluorosis, all associated with work in the potrooms of the Al smelting industry using the Soderberg process. None of these potroom-related diseases is associated with exposure to Al dust or fumes. These recommendations were followed.
3. With reference to the Gilks and Churg case report linking a case of fibrosis with aluminum fibers, Thériault further stated that "... there is little exposure to aluminum, (and aluminum fibers if they exist) in potrooms." This point was clarified in the text of the literature review.

4. Cherry limited her points to the "... larger issue of adequacy of existing data to address the question of occupational exposure and neurological disease". All of her textual criticisms were relevant, and are reflected in the revised text of the literature review. These were all additions and clarifications, not generally corrections. She brought up some questions which the literature could not answer, however. These included: the adequacy of existing study designs to be able to conclude that aluminum exposure can produce dementia; and the limits of interpretation of the Martyn ecological study from England and Wales (aluminum in drinking water and dementia before age 65) where no gradient of increasing risk with increasing Al water content was present. She provided useful references which were followed up and used in the document (e.g. articles by Longstreth, Shalat, Katz).
5. Morgan provided two reports, the second being an opinion on a case report on lung fibrosis in an aluminum polisher (De Vuyst, 1986). On the De Vuyst case report, he stated: "While there is no doubt that the aluminum polisher had lung fibrosis, the evidence that is available would suggest that the type of fibrosis is not that [fibrosis] one sees in 'aluminum lung'... Secondly, the mere presence of aluminum in the lungs does not indicate that the aluminum led to the development of fibrosis." He also emphasized that aluminum oxide does not cause fibrosis. This discussion was reflected in the text.
6. Regarding the entire document, Morgan stated: "... the report is on the main a (sic) up to date, accurate and objective review". He made an important point regarding exposure to transitional forms of alumina in that such exposure occurs in (bauxite) refineries, not in smelters. He stated also that there is some exposure to alumina in the potrooms of smelters during the conversion of alumina to metallic aluminum, but this is not transitional alumina forms. He further added that there is no evidence that these cause fibrosis in man or in animals unless given by intratracheal insufflation. This method is the only way that the total dust load can be delivered to the lung. The discussion in the paper was altered to reflect this.
7. Morgan also stated that he did not believe there is a definite association between pulmonary granulomatosis and aluminum exposure, but he could not exclude the possibility. This is in contrast to desquamative interstitial pneumonitis, for which he felt there was no evidence linking it to aluminum. The text was not altered to reflect these opinions.

8. Spencer's comments were general and textual. One suggestion to include more discussion on sources of Al was followed. However, a suggestion to expand the review on Al tissue deposition and turnover was only marginally followed because it was not relevant to the task of relating aluminum exposure in the workplace to health effects. Recent work on ALS-PD (i.e. amyotrophic lateral sclerosis- parkinson's disease) was included at the reviewer's suggestion. Organic Al compounds were not mentioned as only one reference was found in the literature and this was not relevant to the discussion. All the textual corrections that could be confirmed were incorporated.

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NUMBER OF PAGES TO FOLLOW:- 7

The Health Effects of Aluminium
for the Ontario Industrial Disease Standards Panel

This is a clear, well-written and comprehensive report. In reviewing it I shall first make comments on various points in the text and then address the larger issue of the adequacy of existing data to address the question of occupational exposure and neurological disease.

Page 3, para 3: The statement that aluminium does not accumulate with age seems critical when considering the effects of environmental or occupational exposure to aluminium. Presumably if aluminium is not accumulated (except with renal insufficiency) a small increase of aluminium in drinking water (for example) could not conceivably be associated with increased risk. Elsewhere (page 20, paragraph 2) it is suggested that aluminium in lung tissue and in the brain may increase with age. Indeed on page 11 (third line from the bottom) it is said that increases with age have been reported for all tissues. It would be helpful to have this clarified. Ganrot's distinction between tissue and sub-cellular accumulation served only to confuse me further.

Page 26, para 2: I was left wondering how many of the 13 of the maximally exposed had been found to have "pulmonary abnormalities"; we are given the numbers only for the less exposed.

Page 34, para 2 onwards: I found this section somewhat difficult to follow as I am not well informed in this area. The summary (page

39, last five lines) was very helpful, particularly the statement that the active forms occur only in smelting and processing but not in secondary uses. This statement could perhaps usefully appear earlier; Table 1 (page 36, 2nd paragraph) was not included with the report, and this may have helped to illustrate the point.

Finally, on this section, I wondered (from ignorance) whether the biological reactivity of gamma to eta aluminas was confined to effects in the lung, or whether this was a factor that should be considered in all aspects of exposure to aluminium including, for example, uptake from the gut. If so, perhaps this section should be in the more general introductory comments rather than in the discussion of lung disease.

Page 45, para 1, line 7: The statement that aluminium is not elevated in blood or other tissues in persons with SDAT who have elevated aluminium levels in the brain seems to be rather important. It would suggest that occupationally exposed workers who appear to clear their body burden might have elevations in brain levels that were not detectable before biopsy or autopsy.

The question of whether or not an antecedent event might alter the blood brain barrier so allowing aluminium to enter seems critical and there are a number of places later in the report at which information relevant to this might have been given. For example on page 50, paragraph 2, it is said that individuals from the endemic areas may develop ALS-PD long after their departure. It would be most interesting to know whether the brain aluminium levels of these patients were comparable to levels in those who had developed the

disease while remaining in an area with unusually high levels of aluminium in the soil and drinking water. Similarly it is said (page 53, line two) that patients with boxer's dementia have neurofibrillary tangles with PHFs; it is relevant to ask whether these tangles contain aluminium at the same levels as the SDAT patients. Presumably in the patients with boxer's dementia the insult preceded any aluminium accumulation.

Page 49, para two, third line: It is not clear what is implied by "these areas". Does the discussion refer to the islands of Guam and Rota?

Page 55, para two, line 12: Both here and on page 60 it is implied that a misclassification between Alzheimer and other causes of dementia would lead to bias. This would be the case only if this classification were confounded with the exposure of interest. In general misclassification only dilutes the apparent magnitude of the effect of interest, and reduces the power of the study. Similarly information from an informant is not necessarily biased, although it may be inaccurate; an occupational history (page 63) does not need to be highly reliable for an effect to be identified.

Page 56, para 2, line 3: The predictive value of a positive clinical diagnosis does not follow directly from sensitivity and specificity (it also depends on prevalence) and the word "then" could be omitted with advantage.

Page 57, para two, line two: It is not immediately apparent how the existence of a cancer register helps in the study of dementia.

Page 59. para two: In discussing Martyn's results it might be helpful to mention the numbers of each case type (for example 445 cases of probable Alzheimers); the discussion of 24 cases, though accurate in the validation study, gives a misleading impression of the size of the main investigation. It may also be worth saying that the information on each diagnosed case was obtained only from the CT request form (generally a poor source of information) and that the definition of probable and possible Alzheimer disease was not that now generally used in epidemiological studies of this condition.

Page 59. para 3. line 5: There was in fact no gradient of risk above 0.01 mg/l; those exposed in the highest group had no higher rate than those in the next to lowest.

Page 63. para 1. final sentence: Shalat et al. published information on occupational risk factors as a separate report. The reference to this is included in the list attached.

Page 63. last line: It is true that the associations in the case-referent studies reviewed must be viewed as hypothesis seeking exercises; indeed this is why they were set up. It is not true that a case-control study based on this design could not provide a valid test of a previously stated hypothesis.

Evaluation of the Contribution of Occupational Exposure

I was impressed by the clarity of the discussion on possible causes of Alzheimer's disease, but was not convinced that it was all relevant to the question of the health effects of aluminium. In particular it is unlikely that studies of heredity, immune mechanisms or transmissible infective agents could help appreciably in answering the question of whether or not aluminium exposure was causally related to Alzheimers or other neurological disease. Similarly the section on case-control studies is rather general and does not address the question of whether or not occupational or environmental exposure has been adequately considered in studies with this design. Of the studies reviewed only French et al. (1983) appear to have considered occupational exposure (although Shalat (see above), has elsewhere).

French et al. considered occupational exposure in a series of only 78 cases and Shalat et al., only 98. The power of a study to identify aluminium as a possible cause depends largely on the frequency of aluminium exposure in the population. It is implied that welders may be considered as an exposed group but in our case-referent study of organic dementias (see reference in list attached) only 1.2% of employment was as a welder. With such a frequency of exposure a study of 78 cases could demonstrate only a relative risk of about 12. Even with our larger series of 319 cases of dementias there would have to be a relative risk of close to 5 before such a risk, possibly associated with aluminium exposure, could be determined. Given the infrequency of occupational exposures, except possibly in welders, it seems clear that this question can best be

answered within a cohort that includes a high proportion known to have had exposure; the Ontario miners exposed to aluminium hydroxide dust, for example, would provide such a cohort or alternatively smelter workers with variable exposures to, and presumably absorption of, aluminium.

In agreeing to comment on this review I had expected to find reports of neurobehavioural studies carried out on currently exposed workers. For some years this has been an accepted approach to investigating the neurotoxicity of organic solvents and heavy metal such as lead or mercury. A rapid and non-exhaustive literature search did not, however, identify any such studies. The one study found (Longstreth et al., 1985) concerned only three aluminium smelter workers who had developed a progressive neurological disorder. These three completed a large number of tests including a neuropsychological battery, which showed poor short-term memory and poor performance in visual motor speed. It seems remarkably that no more comprehensive study has been carried out.

In the course of this literature search, three further papers of possible relevance to this review were located, and abstracts of two (Kabayashi et al., 1987 and Katz, 1985) were found in the information system of the Canadian Centre on Occupational Health and Safety; Katz apparently reports two cases of encephalopathy in aluminium workers. The third reference (Grecham et al., 1986) was not available in the McGill system. I do not particularly recommend these studies, but include them for completeness.

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PROGRESS IN OCCUPATIONAL EPIDEMIOLOGY

Proceedings of the Sixth International Symposium on
Epidemiology in Occupational Health, Stockholm, Sweden,
16-19 August 1988

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1988

EXCERPTA MEDICA, Amsterdam - New York - Oxford

DEMENCIA AND SOLVENT EXPOSURE AT WORK

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EXTENDED ABSTRACT

An association between long exposure to organic solvents at work and various types of psychiatric disability, including dementia, has been reported by Scandinavian investigators, notably Axelson et al (1), Olfson & Sabroe (2), Mikkelsen (3) and Lindström et al (4). This important observation still lacks convincing support from elsewhere.

The present investigation of solvent exposure and hospital admissions in men aged 40-69 identified 381 cases with a wide range of psychiatric diagnoses in Montreal (study A) and 319 cases with various types of dementia (ICD-9 290, 291, 294, 310.1 and 331) throughout Quebec (study B). In study A, two referents were chosen for each case, one from non-psychiatric admissions and the other from local electoral lists. In study B, three referent series were chosen, one of psychiatric admissions for causes other than organic psychosis or cerebral degeneration and two of non-psychiatric admissions. Thus, in all, this study comprised 2278 subjects, 141 men appearing as either case or referent in both A and B.

A telephone interview was carried out with 83.0% of subjects or, where necessary, a family member. A further 9.6% completed a short form by mail. Some job information was available, if only from hospital or electoral records (5.6%), for 98.2% of the sample.

Intensity of exposure was graded using a ten point scale, 0/0 to 3/3, analogous to that used for classification of radiographs. The assessment was made in two ways. One of us (FL) coded each job description taking account of both reported and likely exposures. This method resulted in lifetime histories of exposure that reflected the detail recorded in the questionnaire. A second estimate of exposure was obtained using the reported job titles only. An international panel of three experts assessed the probable exposure to solvents in 131 job title groups selected from the Canadian Classification of Occupations (5). The median rating of each group was used to compute exposure indices parallel to those derived from the rating of individual work histories.

In this paper an intensity grade 2/1 or above for at least 10 years was used to identify those with substantial exposure.

Study A was designed to investigate whether subjects admitted to psychiatric hospitals had more occupational exposure to solvents than the general hospital referents. The odds ratio calculated from this sample was 0.97, suggesting that general psychiatric patients were not at increased risk; further analysis of these data is required to confirm that no diagnostic or exposure sub-group was an exception to this conclusion. Study B was undertaken to compare the solvent exposure of those with organic brain damage with that of other psychiatric patients. In this study the odds ratio for solvent exposure was elevated when exposures were estimated using individual assessments (OR = 1.46; 90% CI 1.05 - 2.04); analysis based on job title gave a similar result. Patients with a diagnosis of dementia associated with alcoholism were at highest risk with an odds ratio of 5.7, based on 20 discordant pairs.

ACKNOWLEDGEMENTS

This study was funded by the Institut de recherche en santé et sécurité du travail du Québec. The analysis of study A was carried out by France Labrèche as part of the work for her doctoral thesis.

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Dear Dr. Heller:

At your request I have reviewed The Health Effects of Aluminum which was written by Lesbia F. Smith. Let me say from the start that I feel the report is in the main a up to date, accurate and objective review. Most of my criticisms are relatively minor. I shall give attention to those statements which I feel are inaccurate or which need to be amended.

On page iii of the Executive Summary in Paragraph 6, the statement occurs "However, exposure to low temperature transitional forms of alumina in smelting may produce lung fibrosis." This is inaccurate for several reasons. Firstly, exposure to the transitional forms of alumina occurs in refineries, not in smelters. It is true that there is some exposure in the pot room to alumina in smelters when the alumina is being converted to metallic aluminium, but to my knowledge exposure to transitional forms of alumina does not occur. Exposure to the transitional forms of alumina occurs in bauxite refineries. There is, however, no evidence whatsoever that low temperature transitional forms of alumina ever induce lung fibrosis in man. Neither have such forms been shown to induce fibrosis in animals when given by inhalation, however, when given by endotracheal injection they may do so. I believe that if Dr. Smith goes back to our Chapter in Gitelman, she will see that we emphasize this fact.

Turning to page IV of the Executive Summary, I would be inclined to emphasize that although pulmonary alveolar proteinosis, aluminium fiber induced pulmonary fibrosis, and desquamative interstitial pneumonitis (DIP) have been described in man, the evidence to incriminate the latter (DIP) is, in my opinion, completely absent. Later on in the same paragraph, mention is made of pulmonary granulomatosis. I do not believe that there is a definite association between the granulomatous condition that was observed and exposure to aluminium, nevertheless the Belgian workers conducted a much more thorough investigation of their subjects than did the persons who described the association between pulmonary alveolar proteinosis and desquamative interstitial pneumonitis, etc. Although I think it unlikely that aluminium induces a sarcoid like granulomatous condition in the lungs, I cannot entirely exclude the possibility. The fact that there is so little epidemiological evidence to confirm their hypothesis is against the possibility, nevertheless, I believe that one cannot entirely dismiss this hypothesis. In the same paragraph mention is made of aluminium hydroxide powder being used in the prophylaxis of silicosis in Ontario; this statement is not true. What was used was metallic aluminium, however, the metallic aluminium is oxidized immediately on exposure to air and there was a thin layer of aluminium oxide over the metallic aluminium rendering it innocuous. I do not believe, however, it is appropriate to describe the material that was inhaled as aluminium hydroxide powder.

The statements in regard to the neurological effects of aluminium, namely paragraphs 11 and 12, seem to me to be accurate and I have no suggestions to make.

The chemical and physical properties, the balance studies, etc. appear to be accurate and comprehensive.

Turning to page 9 in the bottom paragraph dealing with uptake from the lungs, again it is stated that aluminium hydroxide is used as a prophylaxis against silicosis. It would be better to say prophylactic and here again it is not aluminium hydroxide dust, but aluminium metal.

On page 14 there is a description of "Meaningful biologic monitoring presupposes that four conditions be met". I do not know who Dr. Aitio is, but he is guilty of tautology and circumlocution. The phrase would read much better, "Biologic monitoring requires that four conditions

be met" rather than what he wrote. To write of meaningful and meaningless biologic monitoring is devoid of "meaning". Of more import, however, is the first condition. I do not believe that it is accurate to say that it must be possible to monitor the concentration of substance or its metabolites in body fluid, etc. In many a instance one has to rely on monitoring the response to the particular agent. To imply that taking serial x-rays in subjects who are exposed to asbestos or silica is not biological monitoring and is, in my opinion, inaccurate. I wonder why Dr. Aitio (and Dr. Smith) feel that his definition is better than that put forward by the World Health Organization! There are an excellent set of criteria that have been formulated and published by the World Health Organization and which should be applied to all screening programmes and which are both more complete and phrased in better English. Similarly, regarding condition 4, namely, "The result can be interpreted in a meaningful way." is sheer jargon. This should read "The results are valid". One cannot interpret results in a meaningless way. I do not mean to be picayune, but this series of quotes from Dr. Aitio is a bit too replete with jargon for my liking.

Turning now to Aluminium Related Health Effects on page 23 under the discussion General, Stokinger's name is spelled incorrectly. In the following line, mention is made of a skin condition called erythema. The term "erythema" simply means redness and there is no such skin condition called erythema. I think it would be better to label the condition as "photosensitive dermatological disorder associated with irritation and itching".

Turning to page 24, in the first paragraph it mentions that "Fumes from soldering operations can result in the delayed- type asthma, similar to pollen allergy." I believe most people would say that pollen allergy is an IgE mediated response, i.e. an immediate reaction not a delayed reaction. While it is true that soldering operations can result in delayed type asthma, but the comparison to pollen allergy is incorrect.

On page 25, under Section 4.2 The Lung, the second sentences reads "These are not absorbed, but rather are retained in the lung, possibly transported by respiratory macrophages, etc.". This statement is not entirely accurate. Many particles that have been deposited in the alveoli are picked up by macrophages and the macrophage migrates to the mucociliary escalator where it is subsequently carried to the larynx and coughed up. Other particles are removed by the macrophage through the lymphatics and carried to the regional lymph nodes. The statement as it appears now is misleading since although it

mentions the respiratory macrophages being transported and coughed up, earlier it states that the particles are retained in the lung. This is somewhat oxymoronic and contradictory.

On page 26 in the Case Report on line 6, it says "with rapidly progressive encephalopathy". I think it would be more accurate to write that as "who developed rapidly progressive encephalopathy". Similarly, on page 27, in the description of McLaughlin's case, mention is made of explosives and aluminium powder in shells. At that time the war was over and most of the aluminium was used in fireworks rather than in shells. I believe that was true of the factory that Mitchell and McLaughlin had studied.

On page 28 the last sentence of the first paragraph reads "In the United States, only stearic acid was used and no case of "aluminosis", has ever been reported, not was ever reported. This again is not entirely true. A couple of cases have been reported, but they are not convincing and the association is almost certainly spurious.

Turning to page 30, the subject described by Miller et al was indeed a grinder. We (Dinman and I) did not challenge the findings of Miller because the particles produced by grinding would not have been respirable - they certainly could. Grinding will frequently produce respirable particles, especially if the grinding wheel is revolving rapidly. Under such circumstances the particles that are produced by the process are irregular and of all shapes and sizes. As one looks at them under the microscope they tend to be jagged. I would refer Dr. Smith to the original description by Miller and I especially would ask her to look at Figure 4 in their case report. This shows spherical aluminium particles of varying size, but all are microspheres. This is also mentioned in the text. The only manner in which spherical particles would be formed was if the aluminium were given off in molten form, i.e. as a liquid aerosol. Subsequently when the particles cooled down in the air they would form spheres. It is much more probable that the subject of the report was inhaling fumes from somebody near him who was welding aluminium. We do not dispute the diagnosis of PAP in this case report - which is a nonspecific response - and are willing to accept that the fumes to which this man was exposed were responsible, but one cannot attribute it solely to the inhalation of aluminium. The latter has been shown in animals to lead to the development of PAP.

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On page 31, the name is De Wyyst. I do not believe there is an "i" in it.

Turning to page 36, I note mention is made of Table 1. I did not receive a copy of this table.

On page 37, the term MMEFR is used. This is outdated and it would be more correct to refer to this as the FEF₇₅. The last sentence in the first paragraph ends with "Many workers had been miners, or had pulmonary TB, etc.". I do not believe it is accurate to say that many had pulmonary TB and this should be checked.

On page 38 mention is made of the paper by Townsend et al. I think it would also be appropriate to include the earlier paper by Townsend and co-workers as this described in more detail the lung function abnormalities in the same group of workers described in the 1988 paper. I believe the earlier reference should be included (Am Rev Resp Dis, 132, 1174, 1985).

On page 39, at the bottom of the page in the last five lines, the statement is made that "There are alumina species which can cause pulmonary fibrosis, in particular, active low temperature transitional forms of alumina. These can occur in the smelting and processing of aluminium but not in its secondary uses." I do not know where Dr. Smith obtained the evidence for this statement. These forms of alumina were shown to produce pulmonary fibrosis in animals on endotracheal injection, but not on inhalation. They have never been shown to cause fibrosis in man. In this connexion, the animal experiments were carried out by King and his co-workers, who were stimulated to look further at alumina following the description of Shaver's Disease. Prior experiments conducted by King and Leroy Gardner, as far as I can recall, revealed no pulmonary fibrosis. Moreover, such exposures do not occur in smelting but in aluminium refineries. Dr. Smith needs to differentiate between refineries and smelters, where the processes are entirely different.

Turning now to the Neurological Discussion, I wonder whether Dr. Smith might like to emphasize that over the last 30 to 40 years, huge amounts of aluminium hydroxide have been used in the treatment of peptic ulcer. When I first graduated, long before H1 and H2 antagonists, etc. came into use, persons were given intragastric aluminium hydroxide by drip and thus the description of an atypical motor neurone

disease due to facial cream seems extremely tenuous and the association completely fortuitous. Were there any connexion between motor neurone disease and the injection of aluminium, this should have been evident years ago.

On page 44, mention is made of "definitive evidence of the cause of an organic cognitive defect is pathological examination of the brain." I wonder if this statement is entirely correct since in many instances examination of the brain does not produce definitive evidence of such a defect.

I really have very little else to add and I believe that the review, provided the changes I have suggested are made, will be both accurate and contemporary.

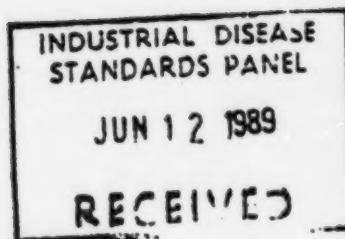
Finally, I have one or two other minor points relating to one or two words which are used by Dr. Smith and which I believe are not preferred English. First, the use of the word compensable is unacceptable to the purist. Subjects are not compensated, they are compensated and therefore the disease is a compensatable disease and not a compensable disease, but I agree that at least in the U.S. the distinction is not made.

Yours truly,



W. K. C. Morgan, M.D.

WKCM:k





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June 23, 1989

Dr. James G. Heller
Executive Administrator
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Industrial Disease Standards Panel
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Toronto, Ontario
M5C 1C3

Dear Dr. Heller,

Dr. Smith rang me up today mentioning that there was an additional paper to which I had not referred and which purported to show that lung fibrosis could result from working as an aluminium polisher. This appeared in the European Journal of Respiratory Diseases, volume 68, page 131, 1986. A facsimile of the paper was transmitted to me. Page 135 seems to be missing. Nonetheless, I have read the remainder of the paper and as far as I am concerned, it in no way influences my prior opinion.

Firstly, there was little evidence that indeed the fibrosis was related to exposure to aluminium. While there is no doubt that the aluminium polisher had lung fibrosis, the evidence that is available would suggest that the type of fibrosis is not that one sees in "aluminium lung". Thus, it did not involve the upper regions of the lungs and it had obviously been present for a long time since there was honeycombing at the bases of the lungs along with a fair amount of fibrosis in the mid zones. Secondly, the mere presence of aluminium in the lungs does not indicate that the aluminium led to the development of the fibrosis. There is no reason to assume aluminium polishers are immune or exempt from developing fibrosing alveolitis, eosinophilic granuloma etc. Moreover, exactly the same situation applies in that if he was exposed to metallic aluminium particles, the dust would be immediately coated with aluminium oxide and as such would not be fibrogenic. The development of a bronchial adenocarcinoma is quite frequently seen in all types of fibrosis ranging from asbestosis to scleroderma and also in fibrosing alveolitis. There is a reflection of increased cellular activity present in the lungs. As for the mineralogical studies, I think it has to be borne in mind, if you put a monkey in a cage and expose it to aerosolized particles, be they solid or liquid particles, such particles will settle in the lungs and since not all are removed, some will remain there. This certainly applies to aluminium metal, especially when it is coated with aluminium oxide in corundum, and when

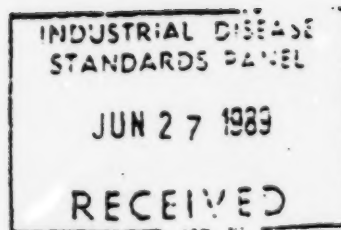
Page 2

used as an abrasive. This does not mean that the fibrosis in any way arises as a result of the presence of the metal. Moreover, the differentiation of EDXA of aluminium from aluminium oxide is not possible, although the investigators in this case talk of using optical methods. In short, I do not find this case history compelling and I do not believe that aluminium was responsible. Perhaps you would be kind enough to convey my response to Dr. Smith.

Yours sincerely,

W.K.C. Morgan, M.D.

WKCM/kg



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Center for Research on Occupational and Environmental Toxicology
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Telephone: (503) 279-4273
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July 18, 1989

FAX No. 416 324-4536

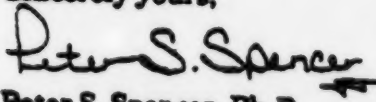
James G. Heller, Ph.D., D.E.C.H.
Executive Administrator
Ontario Ministry of Labor
10 King Street East
Toronto, Ontario, M5C1C3
Canada

Dear Dr. Heller:

Please find enclosed a review of The Health Effects of Aluminum prepared in association with my colleague Dr. Glen Kisby. I regret this review is arriving later than you wished.

Thank you for inviting my comments.

Sincerely yours,



Peter S. Spencer, Ph.D.

PSSjt

Enclosure

Schools:
Schools of Dentistry, Medicine, Nursing

Clinical Facilities:
University Hospital
Doernbecher Children's Hospital

Child Development and Rehabilitation Center
University Clinics

Special Research Divisions:
Vollum Institute for
Advanced Biomedical Research

Center for Research on
Occupational and Environmental Toxicology

A Review of the Health Effects of Aluminum

1. GENERAL COMMENTS

This provides useful oversight for those in occupational and environmental health on the biological properties and adverse effects of aluminum (Al) and its compounds. The document has some weaknesses: (1) sources of Al are not specified in detail; (2) tissue deposition and turnover at binding sites is scantily considered; (3) recent work on Guam ALS/P-D is omitted; (4) organic Al compounds (if any) are not considered; (5) heavy reliance is placed on review articles, rather than dependence on the author's reading of original communications; (6) certain citations (i.e., those in the Skalsky and Churchman (1983) article) are omitted from the bibliography.

2. SPECIFIC COMMENTS

p. iv, para 8. Specify type of neurological disease.

p. v, para 10. Two major hypotheses exist for the etiology of Western Pacific ALS/P-D: both have been seen as either competing and complementary, since medicinal use of cycad seed is the only common use of this plant in the three high-risk areas of ALS/P-D (including Guam, where the seed has also been used as food), the phrase "food toxin" should be replaced by "plant toxin". Incidence of ALS/P-D is hypothesized to be decreasing because of changes in the medicinal and food practices in these areas.

p. v, para 11. "plant" not "food"

p. v, para 12. Al is found in the neurofibrillary tangles of Guam ALS/P-D.

p. 2, line 8. Dr. Tom Clarkson of University of Rochester may have radiolabeled Al.

- p. 2, lines 13-16. Explain "quite difficult". State accuracy of existing measurement methods and compounding variables thereof. Address the widespread distribution of environmental Al and problems this presents for accurate estimation of Al. How do inaccurate measurements impact the interpretations of human health effects ascribed to this metal?
- p. 3, line 2. "unusually" means "heavily"?
- p. 3, line 6. Deposition and turnover of Al in tissue are also critically important pieces of information
- p. 3, line 13. Specify meaning of "age", and to which organs this statement applies.
- P. 3, lines 16-19. Which studies are reliable; which are not, and why? Who has made the latter judgement?
- p. 3, line 23. Absorption from where?
- p. 4, line 6 Source of dietary Al?
- p. 4, line 8. Which vaccines contain Al? Is this of significance relative to other sources of Al exposure?
- p. 4, line 11. Aluminum trioxide?
- p. 4, line 22. From which part of the gut is Al absorbed?
- p. 5, lines 1-2. Absorption of metals varies with particle size and volume of the medium in which it is distributed. Has Al absorption been studied in relation to these factors?
- p. 5, line 4. Which part of the intestine?
- p. 5, line 10. Specify meaning of "actively carried".
- p. 8, line 18. What is the limited evidence? Is it confined to the case report on p. 9?
- p. 9, para 2. Detailed description of this case is needed. What was the composition of the vehicle? Is there experimental verification of Al transport across skin under controlled conditions? Was the subject's skin normal?
- p. 9, line 17. Was evidence of Al uptake from Al oxides sought?

- p. 9, line 19. Use of Al hydroxide as a prophylaxis against Silicosis is unclear.
- p. 11, line 19. Specify meaning of brain parts.
- p. 12, para 1. How is Al bound to, and released from bone? Is Ca involved? Are there conditions (acidosis?) where Al release would likely increase?
- p. 12, line 16. Explain basis for increase in biological half-life of Al with long-term (how long?) exposure.
- p. 12, line 21. If Al is bound to bone and brain, why is there no retention by these tissues under the conditions stated?
- p. 12, line 24. Does this sentence refer to the human, and what is the meaning of "aged"?
- p. 13, line 6. What is the meaning of "toxic" in this context? Does the term refer to cytotoxicity or some response specific to brain cells (nerve cells)?
- p. 16, line 13. Explain "encephalopathy" briefly.
- p. 18, line 23. Specify meaning of "stabilized".
- p. 19, lines 3-6. Citation needed.
- p. 19, para 2. Were these patients given neuropsychological exams before and after DFO? What were the results?
- p. 19, line 22. If Al accumulates in bone and brain (p. 20), this statement requires qualification.
- p. 20, line 6. Is the evidence for brain Al elevation with age conclusive?
- p. 20, line 9. Specify "case".
- p. 21, line 1. Vehicle volume and particle size are also likely to be relevant.
- p. 21, lines 23-25. To whom does this statement apply?
- p. 21, line 24. To whom does the statement about maltol apply?
- p. 24, line 9. What is known of the biological basis/toxic mechanism of Acroanesthesia?
- p. 29, line 11. Substitute "encephalopathy" for "neurological disease".

- p. 30, lines 14-16. Is this hypothesis credited to the reviewer?
- p. 36, lines 10-12. Spell out why.
- p. 41, line 4. Substitute "encephalopathy" for "neurological disease".
- p. 42, line 3. Neuropathological findings available?
- p. 42, lines 4-7. *ACTA Neuropathologica* 1-2 years ago carried an article contrasting the neuropathology of FDAT with DD.
- p. 42, line 4. Doesn't the author mean that these are the only non-dialysis dementia cases to link Al absorption with tissue deposition?
- p. 42, lines 7-13. Total composition of facial cream? Clinical picture prior to and following DFO treatment?
- p. 42, line 19. "May have resulted" would be appropriately conservative.
- p. 44, line 14. Abnormal CAT scans are predictive of what?
- p. 45, para 1. Controversial area! Dr. D. Perl (cited) recently stated that Al levels in SDAT are not consistently elevated. (A call to Dr. Perl at Mt. Sinai hospital Medical School in New York might help.)
- p. 45, para 2. It is critically important to separate the non-specific nerve cell changes (increased 10nm intermediate filaments - I.F.) induced by Al introduced into brain or CSF (or orally- see Garruto et al.), from the Paired Helical filaments (P.H.F.) found in SDAT and Guam/Japan ALS/P-D. I.F. can be increased by a number of chemically unrelated substances (acrylamide, hexanedione, propionitrile), and they differ structurally and biochemically from P.H.F.. P.H.F. have been induced experimentally once by DeBoní and Crapper in nerve cells in culture exposed to a medium high in glutamate/aspartate.
- p. 45, line 6. Meaning of "high"? Which other metals have been found?
- p. 46, line 12. Specify parts of brain; see note above re: Dr. D. Perl.
- p. 47, line 11. See also *ACTA Neuropathologica* article above.
- p. 48, line 1. How widely is this hypothesis accepted?

p. 49, line 7. Histopathology of ALS/P-D in New Guinea (Irian Jaya, Indonesia) has not been studied. The neurofibrillary tangles contain P.H.F., and senile plaques contain an Amyloid core. The latter have been seen in Guam cases, and these data have yet to be published.

p. 49, para 2. New data from University of Guam (Zoland and Ellis Neill) show that Guam rivers (traditional water supply) are hard waters containing typical calcium concentrations. Traditional food on Guam contains adequate calcium and magnesium and variable concentrations of aluminum (McLaughlin and Steele, unpublished).

p. 50, para 1. Cycad seed was used for medicine in all three high-risk ALS/P-D areas; also for food on Guam. Cycad, a neurotoxic plant, contains a number of potentially toxic chemicals, including β -N-methylamino-L-alanine (BMAA) In large doses BMAA elicits a disease in monkeys with features reminiscent (but not identical to) ALS/P-D. BMAA apparently increases absorption of Al according to McLaughlin (unpublished). The cycad hypothesis appears to be a leading contender for the etiological agent of Western Pacific ALS/P-D but, as Spencer has stressed, the etiological agent(s) in cycad seed have not been identified.

p. 50, line 5. Lathyrism is not similar. While it is an upper motor neuron disease, long latency incubation is not a feature and the disease is largely self-limiting once exposure has ceased.

p. 50, para 2. Note it is generally agreed that one or more environmental toxins trigger this disease.

p. 50, para 3. Not "food" but "plant" (cycad seed is not eaten in the non-Guam, high risk ALS-P-D zones).

p. 52. While there are several examples of familial, presumably hereditary disease, the majority of cases in Sporadic, Calne, et al. (1988) in *Lancet*, proposed an interaction between aging and environmental exposures.

- p. 53, lines 21-22. Spell out examples.
- p. 56, line 6. Guam ALS/P-D provides a solid example of this principle of common environmental conditions provoking a familial disease.
- p. 57, line 15. The neurotoxicity of Al is dependent on species, dose and salt form. Recent studies suggest that oral Al is able to induce non-SDAT-like nerve cell changes in which intermediate filaments accumulate with direct CSF or oral treatment with Al salts (Garruto, et al. 1988 *Lancet*).
- p. 60, line 11. "Inappropriately" or "unusually"?

3. GRAMMATICAL/TYPOGRAPHICAL

- if line 3. "is", not "ia"
- p. 1, para 2, line 3. "0.5", not ".5"
- p. 9, line 6. "Desferroxamine", not DFO
- p. 13, line 8. "weight", not "eight"
- p. 13, line 19. National Institute for Occupational...
- p. 44, line 16. Spell out SDAT - senile dementia of Alzheimer type.
- p. 49, line 4. "AUYU", not "AUJU"
- p. 49, line 5. "JAQAI", not "JOLU"
- p. 56, line 7. "is", not "ia"

14 June 1989

Dr James G. Heller
Executive Administrator
Industrial Disease Standards Panel
Ontario Ministry of Labour
10 King Street East
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M5C 1C3

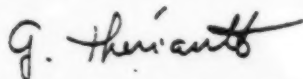
Dear Doctor Heller,

Thank you for inviting me to comment on the document written by
Lesbia F. Smith, entitled 'The health effects of aluminum'.

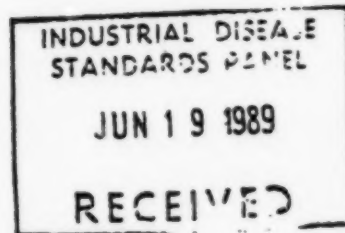
Please find herewith appended my comments. They pertain mostly
to the health of men working in the primary aluminum production
industry.

I hope these comments meet your request. I made them with the
sole purpose of improving this already very good document.

Yours sincerely,



Gilles Thériault, MD, DrPH
Professor and Director
School of Occupational Health



Review of the document entitled 'The health effects of aluminum'
Comments by G. Thériault

Overall, I find this document very instructive: It is clear, easy to read and covers most aspects which come to mind when addressing the question of health effects of aluminum.

My own research activities have given me a good deal of experience in the epidemiology of primary aluminum production workers. I have little preparation in toxicology or in neurology, therefore my comments will focus mostly on health problems among primary aluminum production workers. They will follow the headings as they appear in the text.

EXECUTIVE SUMMARY

This summary reflects pretty well what is written in the report.

I am not comfortable with paragraph 6 on page iii. I think the smelting of aluminum should be kept separate from aluminum ore mining and from secondary uses of aluminum. Several health problems have been reported among primary aluminum production workers (smelter workers) namely lung and bladder cancer, skin telangiectasis and fluorosis. These problems are not believed to be associated with exposure to Al but rather result from exposure to coal tar pitch volatiles and fluoride. I shall comment more later on.

At the end of the first paragraph on page iv, the author refers to aluminum hydroxide powder as used in the prophylaxis of silicosis in Ontario. Nowhere else in the report is this question discussed at length. It seems to me that this is an important topic which has raised controversy and upon which several readers will have worries. I think it should be discussed at length somewhere in the report.

Minor comments: page ii, 3rd line: is instead of ia.

1. INTRODUCTION

No comments

2. CHEMICAL AND PHYSICAL PROPERTIES

No comments

3. ALUMINUM BALANCE

This section being mostly toxicological, I have very few comments.

Page 3, 1st 3 lines: the author mentions that the metabolism of a substance can be studied by time-trend analysis of normal and unusually exposed population. If this refers to animal studies, I think that the word population may create some confusion. If it refers to human population, I think this should be stated in the context of epidemiological studies.

Page 10, 1st para: I think the reference to Morgan and Dirman should be kept for more in depth discussion on the fibrogenecity of aluminum oxyde to be presented later in the report.

Page 13, line 7: 'Normal brain levels range from 0.25 to 0.75 mg/kg wet weight'. This is a repetition.

Page 18, 4th line of the last para: should read benefits.

4. ALUMINUM RELATED HEALTH EFFECTS

4.0 GENERAL

I have some difficulties with this section. None of the risks listed here are due to aluminum exposure. I take the liberty of appending to my comments reprints of 3 papers we wrote, one on bladder cancer and two on telangiectasia in aluminum industry. I think they may help the author to rewrite this section which I feel is not entirely correct.

The making of aluminum is done through an electrolytic process, Soderberg or Prebake. The Soderberg process gives emissions to a large quantity of coal tar volatiles which are believed to cause several health problems including lung and bladder cancer and, possibly, skin lesions. This is much less true with the Prebake process. However, with regard to skin telangiectasis, we are not certain of what the causal agent is. We noted that this phenomenon was a lot more prevalent on people working close to or inside the reactor cells.

With regard to the ischemic heart disease which is referred to by the author, it is true that we observed a somewhat higher risk among Soderberg and Prebake workers compared to other aluminum workers. However, we were unable to relate this to any particular exposure at the workplace. In my opinion, it is still too early to say whether or not this increase in ischemic heart disease can be attributed to working in aluminum industry. In any way, this is minor compared to the excess risk of bladder cancer we observed in this industry and which deserves a lot more attention.

4.1 THE SKIN

The author mentions that an anesthetic condition of the fingers (acroanaesthesia) can follow long term contact with aluminum. This is the first time that such a phenomenon is brought to my attention. I know that some cases of Raynaud's phenomenon (vibration white fingers) have been reported in aluminum smelting industry and that people have pretended that vibration and heat contributed to this phenomenon. This, again, has nothing to do with exposure to aluminum itself.

In the first 5 lines of page 25, I am not sure what the author is referring to in linking telangiectases with spider neavi encountered in liver diseases. We did analyse the relationship between ischemic heart disease and skin telangiectases because aluminum workers affected by telangiectases did worry of a potential association with heart disease and because a larger proportion of these workers had shown abnormalities on their ECG in a previous investigation. However, it seems to me that this is irrelevant in the context of the present discussion.

4.2 THE LUNG

No comments

4.2.1 CASE REPORTS OF LUNG EFFECTS

5. PULMONARY FIBROSIS AND ALUMINA FIBERS

Like everyone else, I was quite surprised by Gilks and Churg report of a case of pulmonary fibrosis in an aluminum smelter worker. This is a rather unique case I am afraid. In my opinion, there is little exposure to aluminum (and aluminum fibers if they exist) in potrooms.

4.2.2 EPIDEMIOLOGY OF LUNG DISEASE IN ALUMINUM MINING, PROCESSING AND HANDLING

2. SMELTER WORKERS

Chan Yeung and Martin studies do not refer to aluminum toxicity. What they are observing is related to coal tar pitch volatiles exposure. This may be different from Townsend's study who seems to have referred specifically to exposure to alumina.

4.3 THE CENTRAL NERVOUS SYSTEM AND ALUMINUM

It is mentioned in section 4.3.1 that no case of neurological disease or syndrome was uncovered in any of the exposed workers

... To my knowledge, this is correct, although it does not necessarily mean that such problems do not exist; it is simply that they have never been looked for carefully. Neurological diseases such as Alzheimer, are not coded specifically as cause of death. There are no registries of such diseases. Therefore, it may very well have happened that they just were overlooked.

I am not in a position to comment further on neurological or mental diseases.

Minor comments: page 56, line 7: read is instead of ia.

Page 58, line 14: read age adjusted mortality rate instead of mortality rate for age related dementia.

Page 63, last sentence: rather strong statement. I think that useful information can come out of case control studies.

Overall, this is a good document. Very instructive. Stronger on toxicological and physiological than on epidemiological aspects. It could be of interest to single out the reports on health of aluminum production workers and to treat them separately because they do not really address the question of the toxicity of aluminum but result rather from the hygienic condition encountered in aluminum electrolytic process environment.

BLADDER CANCER IN THE ALUMINIUM INDUSTRY

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Summary The incidence of bladder cancer is unusually high in aluminium smelter workers. An epidemiological study showed that workers in Soderberg potrooms are at highest risk for bladder cancer, the adjusted overall relative risk being 2.39 (1.34-4.28). Exposure to polycyclic aromatic hydrocarbons, of which benzo(a)pyrene (BaP) served as an indicator, seems to be the causative factor. The relative risk was evaluated at 12.38 for workers with 20 or more equivalent years of BaP exposure. Cigarette smoking contributed significantly to the appearance of bladder cancer in the population studied. There is a synergistic effect when cigarette smoking and BaP exposure are combined; the numbers in our population are too small to determine whether this interaction effect is multiplicative or additive. It is concluded that bladder cancer is associated with aluminium smelting (primarily with the Soderberg process).

INTRODUCTION

In 1981¹ we raised the possibility that working in the primary aluminium industry could be associated with an excess of urinary bladder cancer. This arose from the observation that employment in an aluminium reduction plant accounted for part of an excess of bladder cancer noticed among men in a census division of the Province of Quebec.² In the present study we look further at this association by assessing the increased risk of bladder cancer among aluminium workers exposed to chemicals in the workplace.

METHODS

This study involved five aluminium plants located in different regions of the Province of Quebec. They all produced primary aluminium with use of the Soderberg reduction process (one plant also had some prebaked units). In all plants except one with 7500 men, the size of the workforce was between 300 and 1200.

All cases of bladder cancer (ICD code 188) in men reported over a 10-year period (1970-79) in hospitals from regions where an aluminium plant was operating were collected from the provincial

Tumor Registry and from regional hospitals. The list was submitted to the aluminium companies, who indicated which of the men were current or former employees. For each case, three controls, who had never had bladder cancer, were selected, matched on the following criteria: year of birth, year of first employment in the same company, and length of work at the time of diagnosis of the case. Controls were selected from the same 5-year strata in which the case appeared and matching was done from the computerised information of the aluminium companies.

The companies also provided a detailed occupational history for each man (cases and controls) including, in chronological order, each division, department, and job to which the men had been assigned since the beginning of their employment. Smoking history was obtained from the medical records of the plants' clinics. The environmental hygiene service of one of the companies provided an assessment of tar (estimated by measuring benzene-soluble material (BSM)) and polycyclic hydrocarbons (estimated by measuring benzo(a)pyrene (BaP)) concentration for each of the occupations within the aluminium plants. They corresponded to actual measurements of environmental samples for the more recent years. For earlier years, estimations were made by the company's engineers from their knowledge of past processes and former environmental conditions.

From these data, an index of lifetime exposure of each worker to tar and polycyclic hydrocarbons was created on the basis of estimated concentration of BSM and BaP for each job (values ranging between 0 and 1) multiplied by the time (in years) spent at that job. It was expressed in tar-years and BaP-years.

RESULTS

Over the 10-year period, 488 cases of bladder cancer were found in men from the designated regions. The aluminium

TABLE 1—NO OF CASES BY PLACE OF WORK AND YEAR OF DIAGNOSIS

Year of diagnosis	Place of work					Total
	Arvida	Ile Maligne	Shawinigan	Bessiharnon	Base Comex	
1970	5 (1)	..	1	..	..	6
1971	6 (1)	..	..	..	..	6
1972	7	1	1	..	..	9
1973	7 (4)	..	..	..	..	7
1974	5	..	..	..	(1)	5
1975	8 (1)	..	2 (1)	..	..	10
1976	4	..	..	1	..	5
1977	10	..	1	..	..	11
1978	6 (2)	1	..	..	1	8
1979	15	..	2	1	..	18
Total	73	2	2	2	1	85

Figures in parentheses indicate cases with less than 1 yr experience in aluminium industry

companies identified 96 of these men as being current or former employees. 11 of these were later deleted because the occupational history indicated work experience in the aluminium industry of less than 12 months. 85 cases remained (table I). Most of them came from Arvida, where the workforce is approximately 10 times larger than at any of the other plants. The distribution of tumours was as follows: transitional epithelioma grade I (3), grade II (43), grade III (18), grade IV (21).

The mean age at diagnosis was 61.7 years (SD 9.4). The majority of cases were between ages 45 and 74 (4 were below 45, 3 over 74). The mean age at first employment in aluminium work was 25.2 (SD 7.3). A large proportion of cases (69.4%) started work in the aluminium industry during the decade 1940-49, when the industry was expanding. The latency period (interval between beginning of employment in aluminium industry and diagnosis) was 23.9 (SD 9.8) years.

A higher proportion of cases than controls were smokers (table II). The daily cigarette consumption and the number of years of smoking among smokers did not differ between cases and controls.

The aluminium plant was divided into 8 sections which correspond either to geographical areas of the plant or to similar administrative tasks. These sections were further divided into 164 departments. The risk (expressed as odds ratio (OR)) was calculated for each section. It was also calculated for each department within the 3 sections shown to have an OR over 1.50 (table III). In department D4 (Soderberg reactor rooms) the risk is significant (OR 2.70, 95% confidence interval 1.64 to 4.43).

The risk increases steadily with time worked in this department (table IV). The study of confounding factors by stratification reveals that this risk is not changed by cigarette smoking, length of work, or age (table V).

To assess the association between bladder cancer and chemicals encountered in the plant (tar and polycyclic hydrocarbons), odds ratios were computed for categories of

TABLE II—SMOKING HABITS OF CASES AND CONTROLS

Smoking habit	Cases	Controls
Smokers	61	152
Ex-smokers	7	37
Non-smokers	3	45
Unknown	14	21
Total	85	255

$\chi^2 = 9.217$ (smokers and ex-smokers combined, unknowns excluded)
 $p = 0.002$.

TABLE III—DISTRIBUTION OF CASES AND CONTROLS BY DEPARTMENT*

Section	Department	No of cases	No of controls	OR crude	CI (95%)
Soderberg process	D1 anode service	6	7	2.66	0.91-7.94
	D2 control	2	7	0.85	0.17-4.19
	D3 service	17	38	1.43	0.76-2.69
	D4 reactor rooms (electrolysis)	45	75	2.70	1.64-4.43
Reactor lining	D5 scrubbers	2	0		
	D6 anabranch calcining	0	0		
	D7 lining mixing	1	6	0.49	0.04-4.00
	D8 mechanical maintenance	0	3		
	D9 lining centre	9	13	2.20	0.92-5.27
	D10 maintenance and lining	3	2	4.63	0.89-24.14
Pretake process	D11 alumina unloading and distribution	0	3		
	D12 service and control	5	11	1.39	0.47-4.10
	D13 reactor rooms (electrolysis)	21	46	1.49	0.83-2.68

χ^2 (Mantel Haenszel): 15.4056, $p=0.00009$.

OR = odds ratio. CI = confidence interval.

*For a working experience of 1 year or more.

TABLE IV—RISK ASSOCIATED WITH LENGTH OF WORK IN DEPARTMENT D4

Length of employment (yr)	No of cases	No of controls	OR
<1	40	180	1.00
1-9	12	29	1.86
10-19	12	18	3.00
20-29	18	25	3.24
30+	3	3	4.50
Total	85	255	

OR global crude: 2.70 (CI 1.64-4.43). χ^2 linear trend = 17.3556, $p=0.00003$.

BSM and BaP exposure. These risks increased steadily (tables VI, VII) with estimated exposure. This increase was sharper with BaP than with either BSM or years of work in the aluminium industry (see figure).

Finally, the interaction between cigarette consumption and BaP in the generation of bladder cancer was more than additive and did not reach statistical significance when we tested the multiplicative effect with the Rothman test of synergy (table VIII).

TABLE V—RISK ASSOCIATED WITH DEPARTMENT D4 ANALYSIS OF
CONFOUNDING VARIABLES

Variable	Strata (n)	χ^2 M-H	p	χ^2 Hetero	OR crude*	OR (M-H)	CI (95%)
Cigarette consumption	2	12.7378	0.0004	1.294	2.57	2.66	1.56-4.60
Length of work	2	15.8086	0.00007	1.207	2.70	2.77	1.68-4.57
Age at diagnosis	2	14.9305	0.0001	0.003	2.70	2.87	1.62-4.60
Cigarettes + length of work	4	13.1842	0.0003	3.173	2.87	2.80	1.61-4.89
Cigarettes + age	4	12.1941	0.0005	1.390	2.87	2.85	1.53-4.58
Length of work + age	4	15.6737	0.00008	1.509	2.70	2.77	1.67-4.58
Cigarettes + length of work + age	8	13.5130	0.0002	3.502	2.87	2.86	1.64-5.07

*Unknowns in the category "cigarette consumption" account for the fluctuations in crude OR.

Hetero = Heterogeneity.

M-H = Mantel-Haenszel.

TABLE VI—RISK ASSOCIATED WITH EXPOSURE TO BSM

Estimated BSM yr	Total			Smokers			Non-smokers		
	Cases	Controls	OR	Cases	Controls	OR	Cases	Controls	OR
0	6	65	1.00	6	46	1.00	0	17	..
1-9	57	113	3.95	25	87	3.26	2	15	..
10-19	24	50	5.20	21	36	4.47	1	9	..
20+	18	27	7.22	14	20	6.13	0	4	..
Total	85	255		68	189		3	45	

OR global = 4.50 (CI 1.99-10.19). χ^2 linear trend = 16.7854. p = 0.00004.

DISCUSSION

Several occupational groups have shown an increase of bladder cancer. They include workers in the rubber and cable-making industries,^{3,4} the dye and paint industries,⁹⁻¹¹ leather workers, metallurgical workers, and workers involved in making coal gas.¹² Although suspected, the primary aluminium production industry has never before been clearly associated with an excess of bladder cancer. Our observation of an increase in the risk of this cancer with time spent in the reactor rooms strongly suggests such an association.

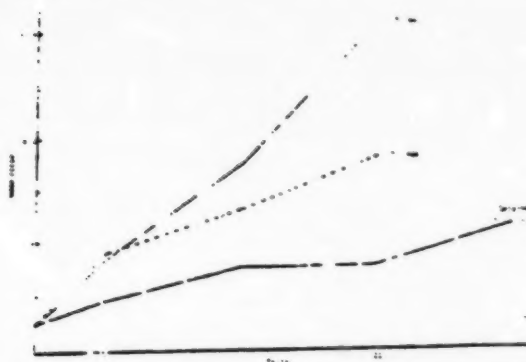
Aluminium is extracted by means of an electrolytic process under heat. The cathode is a steel case lined with a thick layer of carbon. The anode is made of a mixture of pitch and tar

suspended in the electrolytic bath. Several additives (cryolite, aluminium fluoride) are used to lower the fusion temperature and accelerate the reaction. Several air contaminants are emitted during the reaction; they include low and high molecular weight hydrocarbons. Their

TABLE VII-RISK ASSOCIATED WITH EXPOSURE TO BaP

Estimated BaP yr	Total			Smokers			Non-smokers		
	Cases	Controls	OR	Cases	Controls	OR	Cases	Controls	OR
0	6	65	1.00	6	46	1.00	0	19	
1-9	44	140	3.41	32	106	2.31	2	18	
10-19	27	43	6.80	22	32	5.27	1	8	
20+	8	7	12.38	8	5	12.27	0	0	
Total	85	255		68	189		3	45	

OR global = 4.50 (CI 1.96-10.16) χ^2 linear trend = 23.7072, $p = 0.000001$



Risk of bladder cancer according to exposure in aluminium work.

TABLE VIII-INTERACTION BETWEEN EXPOSURE TO BaP AND SMOKING

BaP exposure	Cigarette consumption	
	No	Yes
No	1.00 (1.21)	4.60 (CI 0.66-31.36) (16.73)
Yes	2.50 (CI 0.25-32.02) (2.15)	11.26 (CI 2.15-55.94) (22.97)

Rothman test of synergy: for the multiplicative effect $\chi^2 = 1.90$, CI (95%) = 0.71-5.05

Not in parentheses refer to case controls

concentrations in the environment are measured as benzene-soluble-material and benz[a]pyrene. They range from less than 2.5 to over 600 $\mu\text{g}/\text{m}^3/\text{h}$.⁴

The production and use of several aromatic amines such as 1-naphthylamine, 2-naphthylamine, benzidine, amino-biphenyl, and nitro-biphenyl have been shown to induce bladder cancer.^{15,16} BaP in the environment is a good indicator of the presence and the quantity of the polycyclic aromatic hydrocarbons.¹⁴ The fact that the risk of bladder cancer for aluminium workers rises more steeply with years of BaP exposure than with years worked in the reactor room may indicate that such hydrocarbons or some related constituents have an aetiological role.

The association between cigarette smoking and bladder cancer has been shown in several studies.¹⁷⁻²¹ The risk increases with the quantity smoked. In the urine of cigarette smokers, some tryptophan metabolites have been identified which seem to play a part in the aetiology of that tumour. There seems, however, to be an interaction between cigarette smoking and work in the aluminium industry in the generation of bladder cancer as observed here.

Several other agents appear to be associated with bladder cancer, but a causative role is far from being accepted. They include: artificial sweeteners,²¹⁻²³ coffee,^{24,25} drugs,²⁶ urinary stasis,²⁷ bladder stone,³⁰ parasites,³¹ and nitrates in drinking water.³²

Two processes are used in the production of aluminium—the Soderberg and the prebake. Much less hydrocarbon dust is released in the prebake process, and it is possible that the conclusions of this study apply specifically to the Soderberg process.

The study of the association between lung cancer and BaP exposure was outside the scope of the present research. Such an association is most likely, however, and indeed an excess of lung cancer among aluminium workers has already been reported.³⁴

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Telangiectasia in aluminium workers: a follow up

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Telangiectasia in aluminium workers: a follow up

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ABSTRACT A five step investigation was carried out to gain a better understanding of the morbidity that accompanied the development of telangiectasia on aluminium workers and to find its cause. Fifty workers with multiple telangiectasia when matched with normal controls showed the same amount of illness except that evidence of ischaemia on the ECG was found in nine cases and one control. The cases did not show an excess of abnormal biochemical tests. The basic histopathological lesion affected the surrounding tissue rather than the vessels themselves. Working in the current environment and wearing masks seems to protect young workers from developing the lesions. The Soderberg and not the prebake process was associated with the lesions: the causative agent is probably a gas that contains both hydrocarbons and fluoride components emitted from the electrolytic reactors.

In a previous study¹ we reported the presence of skin telangiectasia on numerous workers in an aluminium plant. The lesions occurred on the upper part of the body (chest, back, shoulders, forearms, neck, and face) and increased in number and size with time spent in the proximity of horizontal Soderberg reactors. Apart from cigarette smoking, factors such as age, personal hygiene, clothing, and exposure to sunlight were not associated with the lesion. In view of the implications raised by this new problem (it had been described previously in the Soviet Union and Poland) we have pursued several lines of research: this paper summarises our most recent findings.

Aluminium is made by an electrolytic process under heat. The cathode is a steel case lined with a thick layer of carbon and the anode is made of a mixture of pitch and tar suspended in the electrolytic bath. Several additives (cryolithe, aluminium fluoride) are added to the reaction to lower the fusion temperature and to accelerate the reaction. Several airborne contaminants are emitted during the reaction, these include dusts and fumes (fluoride and iron particulates, high molecular weight hydrocarbons), gases (carbon monoxide and dioxide, sulphur dioxide, hydrogen sulphide, nitrogen oxide, hydrogen fluoride, silica fluoride, and many low molecular weight hydrocarbons) and radiation

energy from heat and low frequency electromagnetic rays.²

Two processes are used: the Soderberg and the prebake. In the prebake process the anodes are pre-cooked before their introduction into the reactor, thus decreasing sharply the amount of hydrocarbons released into the work atmosphere.³ The agent responsible for the appearance of telangiectasia in the aluminium workers is unknown but since hydrocarbons (tars) irritate the skin and have a particular affinity for organic tissues, they may be thought mainly responsible. The presence of skin telangiectasia has actually been reported in workers at a tar distillery in London.⁴ On the other hand, a group of Polish researchers concluded from their study of telangiectasia in aluminium workers at Skawina that fluorine plays an essential part in their pathogenesis. The purpose of the present study was to search for the causative agent and to look for any illnesses or biochemical changes associated with these lesions.

Methods

The study was conducted in five steps as follows.

Step 1—To determine whether any specific health problems accompanied the presence of telangiectasia, the medical records of 50 workers with more than 100 telangiectasia from our previous 1978 study (cases) were compared with the records of 50 fellow workers with none (controls). Cases and controls were matched on age and seniority. The medi-

cal records were provided by the company's health department, and details of the occupational history were made available by the personnel department. The information was collected by a physician who proceeded in a blind fashion, not knowing which records belonged to cases and which to controls.

Step 2—Physical examination, biochemical tests, and haemodynamic measurements were performed on 50 current workers, 23 bearers of several telangiectasia (cases), and 27 controls. The purpose was to determine whether the cases suffered also from any metabolic disorders. For this part of the study, since some men declined to be examined because of the necessity of a venepuncture, individual matching was not possible. The cases and the controls were therefore treated as two cohorts. The data were obtained by means of a self administered questionnaire and a physical examination by a physician. The haemodynamic tests were carried out by a nurse and the blood sample was taken by a laboratory technician. The investigation took place on the company's premises.

Step 3—Two pathologists from two separate hospital laboratories conducted optic and electron-microscopic examination of biopsy specimens of the lesions. Two men with numerous telangiectasia agreed to participate; in one case immunofluorescence examination was also carried out.

Steps 4 and 5—Aimed at finding the causative agent of the lesions. For the past five years, workers at the plant in Shawinigan, Quebec, have been obliged to wear a mask at work which contained a fluoride captor. All workers who had worked for less than five years at the plant and, therefore, had always worn the mask were examined and the frequency of telangiectasia compared with young workers previously examined in 1978. The purpose was to determine whether dust or fluoride particles

trapped in the mask were responsible for the appearance of the telangiectasia.

Finally we compared the prevalence of workers with telangiectasia at a prebake process smelter with that observed in our previous study at the Soderberg process smelter. A difference between the two might indicate that the causative agent resides in the emissions from the Soderberg process. The prebake process plant was in Lynemouth, UK, a plant with about 750 workers, that started its operations in the early 1970s. The skin examination was carried out by one of the physicians who took part in the previous study.

Results

STUDY OF EMPLOYEES' MEDICAL RECORDS

The cases, and controls were compared on the basis of three variables: social habits, history of illnesses, and results of periodic medical examinations.

The social habits studied were alcohol consumption and smoking (table 1) and no significant difference was found between cases and controls, although in absolute figures there were fewer non-smokers (16 v 22) and more heavy smokers (17 v 13) among cases. Similarly, no significant difference was found for previous illnesses reported although, in absolute figures, the following conditions were diagnosed with greater frequency among cases: ulcer syndromes (13 v 7), haemorrhoids (13 v 9), and obstructive lung diseases (20 v 13).

The periodic medical examination showed that more cases than controls showed signs of ischaemia on their ECG (9 v 1, $\chi^2 = 4.0$, $p = 0.05$). The proportion of ischaemic cases among cases who smoked was 11.8% (4/34) and among control smokers 3.6% (1/28). The group of workers with ischaemia included those whose ECG readings

Table 1 Results from employee's medical records (50 cases, 50 controls)

	Cases	Controls	χ^2 McNemar with correction	p
Social habits				
Regular alcohol consumption	15	12	0.38	0.54
Non-smoker	16	22	1.14	0.29
Heavy smoker (≥ 20 cig/day)	17	13	0.76	0.38
Past illnesses				
Ulcer syndromes	13	7	1.79	0.18
Varicose veins	6	5	0.00	0.76
Inguinal hernias	9	9	0.00	0.80
Haemorrhoids	13	9	0.64	0.42
Periodic examination:				
High blood pressure ($\geq 160/95$)	5	9	0.64	0.42
Hearing loss (≥ 15 db)	28	22	0.00	1.00
ECG $\geq 50\%$ predicted	13	11	0.06	0.81
ECG $\geq 50\%$ predicted	17	9	1.79	0.18
Haemoglobin (< 12 gm/100 ml)	6	1	2.29	0.13
Ischaemia on ECG	9	1	4.00	0.05

made during the periodic medical examination were reported positive by the attending cardiologist and workers who were admitted to hospital for and died of myocardial infarction between 1978 and 1981. There was no significant difference for the other measures such as blood pressure, hearing loss, pulmonary function, and haemoglobin concentration, although in absolute numbers more cases showed FEV₁ below 80% (17 v 9) and a haemoglobin value higher than 17 mg/100 ml (6 v 1) than did the controls.

In this part of the study cases and controls were matched by age and work seniority. The increased rates of cardiac ischaemia and the changes in pulmonary function and haemoglobin values among the cases could thus have resulted from different occupational exposure within the industry.

Clinical investigation

The cases and controls did not differ with respect to age, seniority, cigarette smoking, or tea, coffee, or alcohol consumption.

Table 2 shows the results of the physical examination; there are no significant differences. None of the physicians observed fundal telangiectasia: the ophthalmological abnormalities mentioned were described as increased light reflection, abnormal arteriovenous crossovers, or constricted arteries. They have little importance outside the clinical context and no bearing on telangiectasia.

Table 3 shows the results of the biochemical tests. Since cirrhosis of the liver is sometimes accompanied by telangiectasia several liver function tests were carried out but there were no more abnormalities among the cases than among the controls.

Telangiectasia occasionally occurs in pregnant women and in those using oestrogen hormones. A check for any disturbance in the androgen-oestrogen ratio in workers with telangiectasia was therefore indicated. The mechanism of this disturbance could be either through the direct action of heat on the gonads or by liver toxicity. Hormone levels were not altered in workers with telangiectasia, however, nor

Table 3 Results of the biochemical tests (23 cases, 27 controls)

Tests	Abnormal Tests		χ ²	p
	Cases	Controls		
ALT (GPT) transaminase	0	0	—	—
ALT (GPT) transaminase	1	0	0.01	0.92
γ-GT gamma globulin	1	1	0.00	1.00
Alkaline phosphatase	0	0	—	—
IgA immunoglobulin	0	0	—	—
Direct bilirubin	0	0	—	—
Indirect bilirubin	0	0	—	—
Total bilirubin	0	1	0.00	1.00
Total testosterone	5	5	0.00	1.00
Free testosterone	1	3	0.70	0.40
17 β oestradiol	1	0	0.01	0.92
Intrahepatic alkaline phosphatase	0	0	—	—
Glycohaemoglobin	1*	0	0.01	0.92
Pyridoxine (B ₆)	1	0	0.01*	0.92
Hyaluronidase	2	2	0.00	1.00
Sedimentation rate	1	1	0.00	1.00
Antinuclear antibodies	1	0	0.01	0.92
Protein immunoelectrophoresis*	2	2	0.15	0.70

*One case unknown.

was breast development found on physical examination and libido was not reported to be reduced.

Telangiectasia sometimes accompany autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus, but antinuclear antibody measurements, protein electrophoresis, and IgA measurements were not more frequently abnormal among the cases than the controls. Other variables such as pyridoxine (vitamin B₆), glycohaemoglobin, hyaluronidase, and intrahepatic alkaline phosphatase, believed to contribute to the development of telangiectasia also showed no difference between cases and controls. The same was true for sedimentation rate, blood cell counts, bleeding time, blood pressure, and pulse rate.

MICROSCOPY OF THE LESIONS

The major findings on the optical microscopic examination were the following: dilatation of the capillaries, swelling of the endothelium, the presence of a ring of mononuclear cells around the vessels, slight tumescence or fibrosis of the superficial dermis, and fragmentation of the elastic fibres in the dermis. Under electron microscope, no specific ultrastructural changes were observed, although the endothelial cells were prominent and there was evidence of elastoid degeneration of the collagenous tissue around the vessels. The telangiectasia affected the arteriolar, capillary, and postcapillary venular segments of the terminal vessels. No fibrogen, complement, or immunoglobulin deposits were detected by immunofluorescent studies of the skin biopsy specimen.

Table 2 Results of the physical examination (23 cases, 27 controls)

Physical examinations	Cases	Controls	χ ²	p
Changes in libido	10	0	1.74	0.19
Other skin diseases	2	3	0.04	0.83
Abnormal findings in fundus	10	6*	3.26	0.06
Abnormalities in abdomen	6	2	3.22	0.07
Breast development	0	0*	—	—
Regular intake of medication	—	4	0.07	0.75
Arterial hypertension	2	5	1.00	0.32

*One control unknown.

Table 4 Prevalence of telangiectasia among recent workers

No. of telangiectasia	No. of workers	%
0	40	40.0
1-9	53	46.1
10-19	9	7.8
20-49	5	4.4
≥ 50	5	4.4
Total	112	100.0

RECENTLY EMPLOYED WORKERS' EXAMINATION
All recently employed workers (112) agreed to undergo the medical examination. They were young (75% were under 30), and their personal habits were similar to those of the workers examined previously: 72.2% were regular smokers and 24.3% non-smokers; 12.2% consumed alcohol four to six times a week or more whereas the majority (75.0%) were occasional drinkers and 12.2% never drank alcohol. Only 16 individuals (14.0%) had 10 telangiectasia or more: three men had large lesions (table 4). The comparison between the 1978 and 1981 recently employed workers was made according to the number of years worked either at the plant, in reactor rooms, or in occupations identified in our previous study as being most responsible for the lesions (occupations in which the workers had access to open reactors). As seen from table 5, the most recently hired workers showed fewer telangiectasia than the men hired earlier, given an equal number of years of exposure. Two factors seem to have contributed to this difference, an improvement in the quality of the air in the potrooms; and the mandatory wearing of protective masks by workers in contact with the reactors. The protection offered by these measures does not seem to be fully efficient, however. Workers in at risk occupations for more than one year showed a higher prevalence of telangiectasia than those who had worked for one year or less. Several factors probably contribute to this. For example, workers often remove their masks while working and the masks are not worn outside at risk

Table 5 Prevalence of telangiectasia in Soderberg and prebake processes

	Soderberg % (No.)	Prebake % (No.)	χ^2	p
Worked in the plant (1 to 10 years)	35.0 (123)	7.8 (311)	50.11	1.0**
Worked in reactor room (1 to 10 years)	41.0 (272)	8.1 (148)	49.49	1.0**
Worked in at risk occupations (1 to 10 years)	45.0 (235)	17.5 (63)	15.92	0.6**

areas although the general atmosphere is contaminated.

COMPARISON OF SODERBERG AND PREBAKE PROCESSES

At the time of the survey, the prebake plant had a workforce of 576 men at various locations in the plant. The selection of men for examination was based on work areas and time schedules, and the number examined was 311 (54% of overall workforce, 64% of production employees). The refusal rate was less than 3%. As with the recently employed workers, the comparison between prebake and Soderberg employees was made according to the same number of years worked in a similar environment. Since the prebake process had been in operation for 10 years, no comparison could be made beyond that period.

For equal time worked, a much smaller proportion of workers in the prebake process had telangiectasia compared with workers in the Soderberg process (table 6). This tends to support the hypothesis that the development of telangiectasia may be due to differences in the emissions from the two processes, the most important being the much lower emission of hydrocarbon in the prebake process.

Discussion

CAUSE OF TELANGIECTASIA

The results of this study indicate that fluorides con-

Table 5 Prevalence of telangiectasia in two groups of workers examined in 1978 and 1981

	Tel ≤ 5 mm		Tel > 5 mm	
	1978 % (No.)	1981 % (No.)	1978 % (No.)	1981 % (No.)
Worked at the plant for 3 to 4 years	16.7 (43)	12.4 (47)	9.4 (43)	2.1 (47)
Worked in reactors room for				
< 1 year	24.7 (124)	10.1 (60)**	9.4 (124)	2.3 (60)
1-4 years	23.5 (124)	10.1 (26)	9.1 (26)	2.2 (26)
Worked in at risk occupations for				
< 1 year	20.0 (22)	12.1 (9)**	10.6 (22)	3.8 (9)
1-4 years	26.7 (181)	9.2 (36)*	12.1 (36)	2.8 (36)

*p < 0.05 **p < 0.01

tribute to the development of telangiectasia since the occupations where the lesions are more prevalent involve significant exposure to fluorides. It is also noted that the telangiectasia appear on areas of the body where workers sweat heavily and fluoride is known to be excreted partly in the sweat.⁶ Fluorinated cortisone may produce telangiectasia in exposed patients.⁷⁻¹¹ With the elimination of fluoride, cortisone alone no longer produced the lesions, and a tendency to healing was observed. These observations support the view that fluoride may be a contributing factor in the production of telangiectasia.

On the other hand, there are indications that fluoride is not the only causative agent. Nowhere do published reports on fluorine toxicity mention that fluorides cause telangiectasia, and workers in a fluorine plant in Arvida, Quebec, have not developed telangiectasia. Workers in the prebake process, with the same level of exposure to fluorides as the Soderberg workers, have many fewer telangiectasia and hence it may be that telangiectasia are caused by the association of fluorides with another substance, possibly a hydrocarbon.

HISTOPATHOLOGICAL LESION

The microscopical appearance of telangiectasia suggests that the basic lesion lies more in the tissue around the vessels than within the vessel walls. This view is supported by the appearance in the dermis of fragmented elastic fibres and elastoid degeneration of the collagen. The hypertrophied endothelial cells could be a compensatory mechanism that follows the enlargement of the vessels.

The appearances are similar to those observed in people who develop telangiectasia after topical application of fluorinated cortisone. It was observed that the basic histopathological lesion was a degeneration of collagen, of elastic fibres, and of the basic mucopolysaccharide substance of the dermis.⁷⁻¹¹ This lesion of the interstitial substance of the dermis appears to cause the vascular dilatation observed at the skin surface. If this is so the basic physiopathology is either a stimulation of collagenase that causes an increased degeneration of collagen, or fibroblast impairment that gradually curtails the production of collagen, elastic fibres and dermal interstitial tissue.

From these observations, the hypothesis may be put forward that telangiectasia in aluminium workers result from damage to the fibroblasts accompanied by structural abnormalities of the dermis, together creating lacunae in the supporting structure of the vessels and consequently a widening of the blood vessels which makes them more visible at the skin surface. This theory is strengthened by the inclusion in the phenomenon of all three sections of

the arteriovenous junction—the arterial, the capillary, and the venous. Our opinion coincides with that of Polish workers¹ who supposed that the main pathogenic factor was the disorganisation of collagen and of elasticity, leading to vascular dilatation.

ASSOCIATED ILLNESSES

The observation of ischaemic heart disease in men with numerous telangiectasia deserves special attention. The association of telangiectasia with heart disease is possibly due to chance. No other disease was reported more frequently among the cases than the controls and the biochemical, endocrine, and haematological investigations did not show great frequency of abnormalities. No telangiectasia related illnesses were reported by the cases. On the other hand, there is some suggestion that telangiectasia may be associated with organic and structural changes affecting the entire cardiovascular system, the presence of ischaemia on ECG being one serious manifestation. Russian workers, reporting on disturbances of the blood vessels in the skin and on disorders of the cardiovascular system among reactor workers in an aluminium smelter stated that, "Pathological changes affecting the skin vessels are related to changes in the capillary structure of the conjunctiva of the eyes and to organic and structural changes throughout the cardiovascular system"¹² (translation).

The observation of a high prevalence of ischaemic heart disease in men with telangiectasia should thus not be ignored. More research is required to investigate this association and to assess the extent of any damage to the vascular system as a whole.

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MEDICAL INTELLIGENCE



**SKIN TELANGIECTASES IN WORKERS AT AN
ALUMINUM PLANT**

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OCCUPATIONAL-HEALTH physicians from a large Canadian aluminum company recently noticed the presence of numerous telangiectases on the skin of some production workers. Called to investigate, the Workmen's Compensation Commission confirmed the presence of these lesions. Some affected workers complained of the appearance of the lesions and worried about their effects on health. Researchers from the Soviet Union have reported the presence of telangiectases in workers at an aluminum electrolysis plant,¹ but the lesion has received little or no attention in the Western medical literature.

We attempted to determine whether these skin lesions were related to work in aluminum and to identify the occupations associated with their occurrence. We report here the results of an epidemiologic study among 588 workers in a Canadian aluminum plant. We found an increased number of skin telangiectases on the upper chest, back, and shoulders in 40 per cent of the workers, with an apparent relation between the occurrence of lesions and the duration of occupational exposure. No excess of associated diseases was noted.

METHODS

The plant where the study took place produces primary aluminum with use of a reduction process. It also produces anodes (made of pitch and tar) to be shipped to affiliated firms. It is located in Shawinigan, Quebec, and opened in the early 1940's. Approximately 750 men are employed there at any one time.

All male employees having more than three years of service and at work as of January 1, 1978, were included in the study. The group comprised production workers as well as managers and office employees.

The company provided a list of workers and a detailed occupational history for each of them, including, in chronological order, each division, department, and job to which the men had been assigned since the beginning of their employment. Each worker completed a questionnaire concerning the following: age, clothing (type of garment worn at work and type of material used in the garments), methods and frequency of cleaning and drying clothes, fre-

quency of showers, type of soap used, exposure to sunlight, cigarette smoking, use of respirators, and use of protective equipment at work.

Physicians conducted summary physical examinations of each worker, paying particular attention to the number, size, and location of the telangiectases, to the personal and family medical history, and to drug and alcohol consumption.

RESULTS

The study included 588 (92 per cent) of the 639 men eligible. For various reasons (sickness, leave of absence, or nonavailability) 39 men were not studied. Another 12 records were dropped because of missing information.

The observed skin lesions are shown in Figure 1. They were red to red-bluish maculae or flat patches (often linear in shape) with a maximum diameter of 1 mm to 3 cm. They were painless and nonpruritic, and they disappeared upon finger pressure. When the pressure was removed, the blood was seen reentering the enlarged vessels. These vascular lesions lay within the superficial layers of the dermis, and the skin over them had a normal appearance.

The telangiectases appeared mainly on the upper part of the chest, the back, and the shoulders. Sometimes they were also present on the face, neck, arms, and backs of the hands. They very rarely appeared below the waist and were not found on the nasal or buccal mucosa or in the fundi. Clothing did not affect their distribution, nor was an increased concentration or ring pattern found on the neck or wrists.

The lesions had a characteristic pattern of appearance. In men with less than 10 telangiectases, the most affected part of the body was the upper chest. In those with 10 to 19, the upper of the back was affected as well. Other involved areas were, in order, the neck, the upper arms, the forearms, the face, and the hands.

The lesions seemed to enlarge with time. Pearson correlation coefficients between the total number of telangiectases and the number of large (≥ 5 mm) telangiectases ($r = 0.592$, $P < 0.001$), as well as between the number of lesions and the body surface covered with telangiectases ($r = 0.656$, $P < 0.0001$) were highly significant. Thus, the size and dispersion of these lesions increased as they became more numerous.

Table 1 shows the association between telangiectases and duration of work in the aluminum plant. There is a direct relation; attack rates of telangiectases increased steadily with the number of years worked at the plant. After 25 years, a little over 59 per cent of the men had 10 or more telangiectases, and nearly 35 per cent had lesions that were 5 mm or larger in greatest dimension.

In an attempt to identify the source of the causal agent, the plant was subdivided into four departments: electrolysis, casting, maintenance and service, and management. Study of the association between the presence of telangiectases and the number of years worked in each of these departments revealed that the

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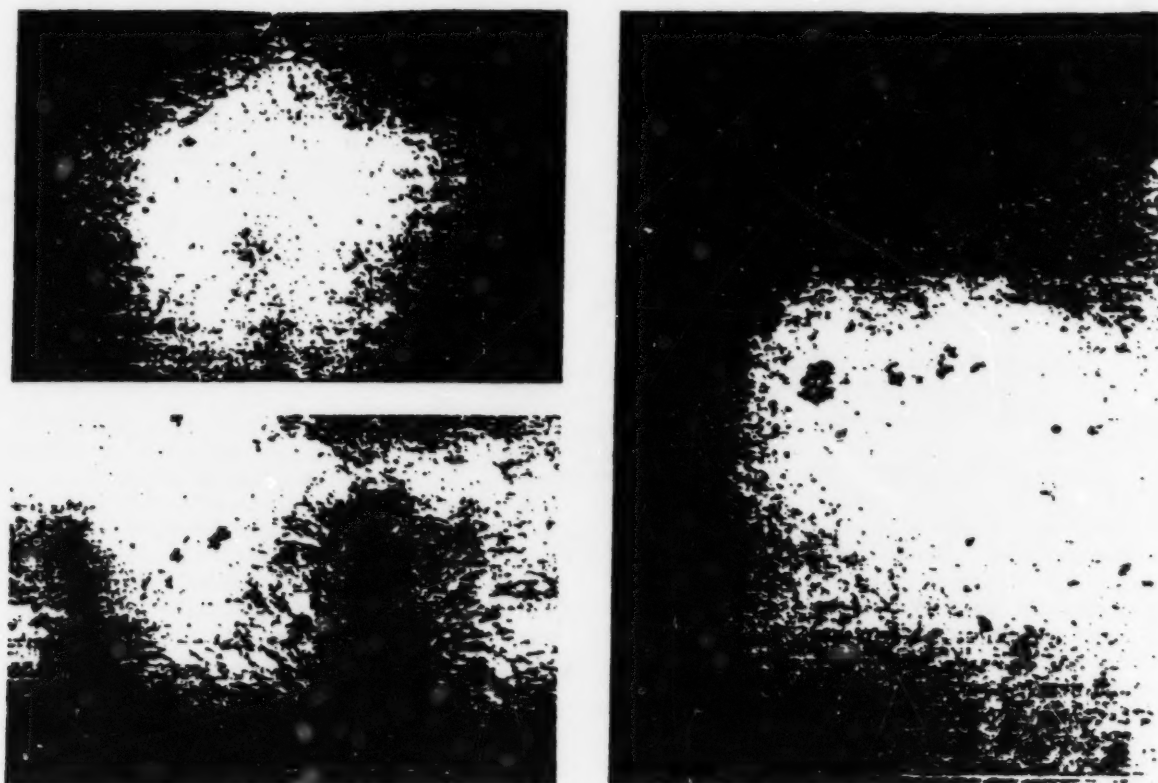


Figure 1. Skin Telangiectases in Workers at an Aluminum Plant.

percentage of workers affected increased with the number of years worked in the electrolysis department only.

In a further search to identify which occupations led to risk, the same association was studied for each job within the electrolysis department. Table 2 shows the increase in the attack rates among men engaged in "at-risk" occupations in the electrolysis department; in those jobs, men work in close contact with open reactors, to feed them, break the crust, extract the aluminum, or handle internal parts of the reactors. The rates increased sharply with time of exposure. After 20 years, nearly all the men were affected (97 per cent had 10 or more telangiectases, and 71 per cent had lesions that were 5 mm or more in greatest dimension).

On the other hand, for persons believed to have never been exposed to these "at-risk" occupations (Table 3), no relation was seen. Some 32 per cent had 10 or more telangiectases, and 11 per cent had telangiectases that were 5 mm or larger.

The telangiectases are not associated with any of the following variables: skin or hair color, exposure to sunlight or ultraviolet rays, frequency of showers, clothing, soap used, respirators, or protective equipment. As for associated diseases, employees with nu-

merous telangiectases reported using drugs (mostly drugs acting on the central nervous system and the digestive system, analgesics, and antipyretics) more often than those with few lesions. They also reported a history of heart disease more often, but this difference was not statistically significant after appropriate corrections for age and cigarette smoking. No other disease was reported to be more frequent among affected workers.

A multiple regression analysis was carried out in an effort to identify any variables other than work in the aluminum industry that might have been associated with the development of the telangiectases. Included were age, cigarette smoking, alcohol consumption, and previous cardiovascular disease. Cigarette smoking was associated with the number of telangiectases. The size of the lesions was associated with both cigarette smoking and age. These associations, however, were much less important than years spent in at-risk occupations. No interaction between cigarette smoking and work with aluminum was found.

Discussion

As described in the medical literature, generalized telangiectases may be divided into four main types: primary telangiectases,^{2,3} secondary telangiecta-

Table 1. Number of Workers with Telangiectases, According to Years Spent at the Aluminum Plant

No. of Years	No. of Workers	No. of Workers with >10 Lesions*	No. of Workers with Lesions >5 mm*
3-4	43	7 (16.3)	4 (9.3)
5-9	80	34 (42.5)	7 (8.8)
10-14	88	33 (37.5)	15 (17.0)
15-19	74	31 (41.9)	11 (14.9)
20-24	44	27 (61.4)	12 (27.3)
25+	239	153 (64.1)	90 (37.7)
Total	588	285 (48.5)	139 (23.6)

*Figures in parentheses denote per cent.

ses,¹⁰ essential telangiectases,¹¹ and spider nevi.¹²⁻¹⁴ The telangiectases in these workers did not seem to fit any of these categories. Clinically, they looked like essential telangiectases, but they differed from this type in that they affected men and showed a body distribution that was unique and consistent from one man to another.

One peculiar feature was the observed association between the telangiectases and the time spent in aluminum production. Dose-response curves showed sharp increases in attack rates with number of years worked. The occupations responsible for the appearance of the lesions turned out to be those that required work near open reactors, indicating that the causal agent might be located within the electrolytic process or its accompanying emissions.

The aluminum-reduction process used in the plant consists of horizontal Soderberg type of reactors only. The pollutants encountered in such a process include dusts and fumes (fluoride and iron particulates, high-molecular-weight hydrocarbons), gases (carbon monoxide, carbon dioxide; sulfur dioxide, hydrogen sulfide, and related compounds; nitrogen oxide; hydrogen fluoride, silica fluoride, and a great number of low-molecular-weight hydrocarbons), and radiation energy from heat and low-frequency electromagnetic rays.¹⁵

Direct contact does not seem to be the mechanism involved in the production of the telangiectases: clothing does not affect their distribution, there is no increased concentration or ring pattern at the neck or wrists, no topical concentrations of the lesions are seen on the chest or in the axillary areas, and a char-

Table 2. Number of Workers with Telangiectases, According to Years Worked in At-Risk Occupations.

No. of Years	No. of Workers	No. of Workers with >10 Lesions*	No. of Workers with Lesions >5 mm*
0	243	78 (32.1)	26 (10.7)
1-4	182	71 (39.0)	22 (12.1)
5-9	54	36 (66.7)	16 (29.6)
10-14	29	25 (86.2)	18 (62.1)
15-19	18	17 (94.4)	13 (72.2)
20+	62	60 (96.8)	44 (71.0)
Total	588	287 (48.8)	139 (23.6)

*Figures in parentheses denote per cent.

acteristic pattern of appearance repeats itself from one worker to another.

Heat alone seems doubtful as the causal agent, since the effects on the skin would have been noticed previously among workers in other trades. It is likely that the causal agent is one or more gases or dusts encountered in the vicinity of the aluminum electrolytic reactors — possibly a hydrocarbon or a fluoride compound acting alone or in combination with heat. Bean has reported that among men who work in the distillation of tar, many have a large number of capillary telangiectases, "far more than found ordinarily in persons not so exposed."¹⁶ It has also been reported that long-term administration of a potent, topically applied fluorinated steroid preparation may be followed by the development of cutaneous blood-vessel abnormalities, notably, telangiectases.¹⁷

A major worry on the part of affected workers was that the telangiectases might indicate the presence of

Table 3. Number of Workers with Telangiectases among Men Never Exposed to At-Risk Occupations, According to Number of Years Worked at the Aluminum Plant.

No. of Years	No. of Workers	No. of Workers with >10 Lesions*	No. of Workers with Lesions >5 mm*
3-4	9	2 (22.2)	1 (11.1)
5-9	10	4 (40.0)	1 (10.0)
10-14	39	8 (20.5)	5 (12.8)
15-19	47	14 (29.8)	3 (6.4)
20-24	21	11 (52.4)	4 (19.0)
25-29	61	19 (31.1)	8 (13.1)
30+	56	20 (35.7)	4 (7.1)
Total	243	78 (32.1)	26 (10.7)

*Figures in parentheses denote per cent.

accompanying diseases. The study did not reveal the presence of any current or past diseases associated with the telangiectases, even though heavily affected workers reported a history of cardiovascular diseases more frequently. After correction for age and cigarette smoking, cardiovascular disease was unrelated to the lesions, probably indicating that the importance of the telangiectases was limited to their appearance.

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